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THE TREATMENT OF CANCER OF THE TONGUE*

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THE relative frequency and importance of cancer of the tongue is indicated by the fact that 21 per cent of all oral cancers occur in this organ. Like most other forms of cancer it is not limited to humans but occurs also in the lower animals, being most frequent in dogs. In both animals and man it ranks second in order of incidence (of oral cancers), the higher incidence in man being explained by the "exclusively human causative factors, syphilis and tobacco."[1]

This form of cancer gains added importance from the fact that with the exception of a few very early lesions surgical procedures have been attended by poor results and these have been secured only at the expense of great mutilation. Nor has there been any very substantial improvement in this respect since the days of Butlin.

With the introduction of radium, hopes were entertained that there would be a great change for the better, but while undoubtedly a change for the better took place, it must be admitted that the early expectations were not fully realized and the improvement was largely due to conservation of tissue as a result of which when radium treatment was successful there was little or no mutilation or impairment of function. So far as cure of the disease is concerned, the published statistics of the end-results of treatment still leave much to be desired, indicating as they do an average of successful results varying between 15 and 25 per cent, some writers even putting the figure as low as 10 per cent.

A further study of many publications, however, brings out the fact that conclusions are being drawn from comparisons made between groups of cases which are not properly comparable. Many of the statistics are heavily loaded with very advanced cases in whom no hope of cure could at any time be entertained and this has cast an unfair and unnecessary cloud of pessimism over the subject as a whole. It seems very obvious that the first essential step towards a better understanding of the general problem must be the adoption of some uniform system of classifying the cases in stages of the disease. This would at least bring into one group those cases for whom there is reasonable hope of cure. The sufferer from *early* cancer is entitled to this degree of encouragement.

Encouragement may also be found in a review of results obtained from the use of methods of treatment developed during the

[1] Martin, H. E., and Holland, B. F. Zoologic distribution of intraoral cancer. *Scient. Monthly*, 1939, *49*, 262–266.

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past few years which appear to show a substantial improvement over those previously secured.

A discussion of the problem from these two aspects forms the subject of the present paper which is based upon the study of approximately 200 cases of cancer of the tongue treated during the past ten years of which 167 have been analyzed in some detail in order to bring out certain points of interest.

CLASSIFICATION BY STAGE OF DISEASE

The desirability of a uniform system of classification by stage of the disease needs no argument. And yet it is a curious anachronism that in a disease so complex and so serious as cancer of the tongue this important step has not received sufficient emphasis to bring about its general adoption. If in cancer of the cervix uteri the cases are grouped in the usual four stages no one would consider comparing the results to be expected in the first or second stage with those in the third or more particularly the fourth. Yet in cancer of the tongue it is still a common practice to group all cases together simply as "cancer of the tongue" as if the problem were the same for all locations and all stages of the disease. The obvious fact is that a small lesion of 1 cm. in diameter on the lateral margin of the tongue without lymph node involvement is so entirely different from a massive, infiltrating lesion with fixed glands that they are no longer comparable problems.

Repeated attempts have been made to devise a system of classification which would combine an accurate description both of the primary lesion and the secondary involvement, but, owing to the fact that these two problems are so entirely different not only in their clinical characteristics but in the treatment required by each and also because it is desirable to have accurate information as to the final outcome of treatment in each, it has been thought better to deal with them separately.

The following method of classification by stages which has been in use for more than ten years has been found simple and may be applied by several observers with reasonable uniformity.

1. *The Primary Lesion*

Stage I: A unilateral or single lesion measuring not more than 1.5 cm. in diameter.

Stage II: A lesion not larger than 3 cm. in diameter with a corresponding degree of ulceration or infiltration.

Stage III: A lesion involving not more than half of the entire tongue or involving other adjacent structures.

Stage IV: A lesion characterized by massive involvement of more than half of the tongue.

2. *Secondary Involvement*

The classification of involvement of regional lymphatics followed is that in general use, viz.:

Stage I: Small, discrete, movable, unilateral, operable.

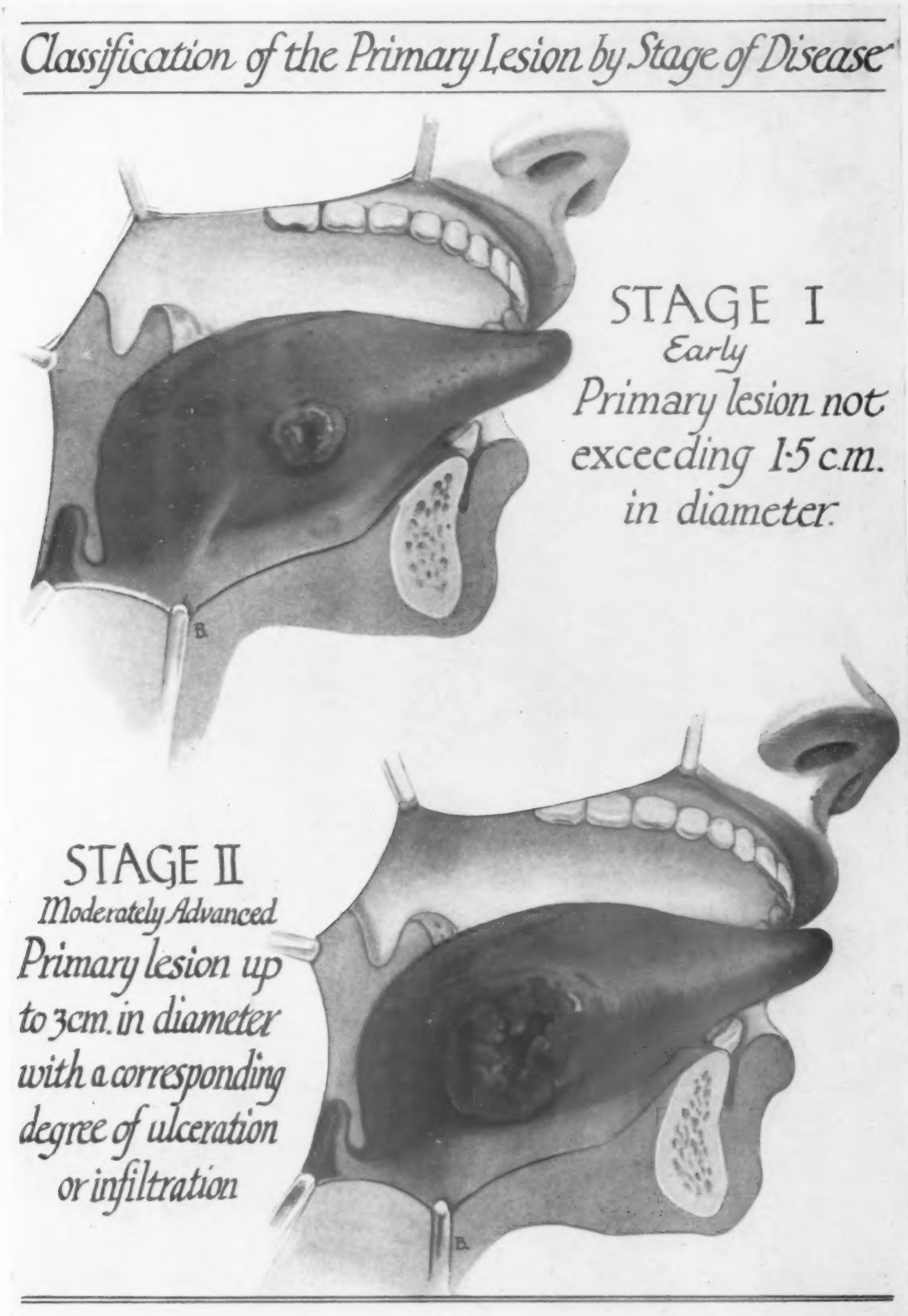
Stage II: Larger, up to the size of olives, still discrete, unilateral; or lymph nodes as described in (1) but which are bilateral. Operable.

Stage III: Massive metastatic carcinoma in lymph nodes, matted and immovable. May be unilateral or bilateral. Inoperable.

AGE, SEX AND STAGE OF DISEASE

Cancer of the tongue is predominantly a disease of males and occurs most commonly in the age group fifty-five to seventy but, like other forms of oral cancer, may occur at almost any age. In this series the youngest patient was thirty-five and the oldest ninety-four, the average age being sixty-two. Further discussion of the bearing of this fact upon end-results will be found later in the paper.

In Table 1 the cases are arranged according to stage of disease of the primary lesion


Classification of the Primary Lesion by Stage of Disease
STAGE I
Early
Primary lesion not exceeding 1·5 c.m. in diameter.
STAGE II
Moderately Advanced
Primary lesion up to 3cm. in diameter with a corresponding degree of ulceration or infiltration

Paintings in color by Douglas Baker

FIG. 1

Classification of the Primary Lesion by Stage of Disease.

STAGE III
Far Advanced
A lesion involving not more than half of the entire tongue OR involving other adjacent structures.

STAGE IV
Very Far Advanced. Massive involvement of the entire tongue.

Paintings in color by Douglas Baker

FIG. 2

TREATMENT OF CANCER OF THE TONGUE
Lesion base of tongue, right side. Three Portal Technique.

Portal No. I.
Right Lateral

Portal No. II
Left Lateral.

Portal No. III
Submental.

Carcinoma Base of Tongue
Right Side. Stage II

FIG. 3

TREATMENT OF CANCER OF THE TONGUE
Lesion left lateral margin. Four Portal Technique.

Portal Nº I
Right Lateral Anterior Oblique.

Portal Nº II
Left Lateral Anterior Oblique.

Portal Nº III
Submental.

Portal Nº IV
Left Posterior Inferior Oblique.

FIG. 4

on admission and also according to sex. It would seem obvious that the highest percentage of successful results should be secured in the first two stages which include all of the early and moderately advanced cases, whereas in the last group, cure of the disease is not to be expected and the only benefits which may be derived from treatment are palliative. It will be seen from the table that the ratio of females to males affected is 1 to 4 which may find an explanation in greater personal care in matters of mouth hygiene. Once the disease is established, however, the discrepancy ceases and the clinical features, course and response to treatment appear to be identical for the two sexes.

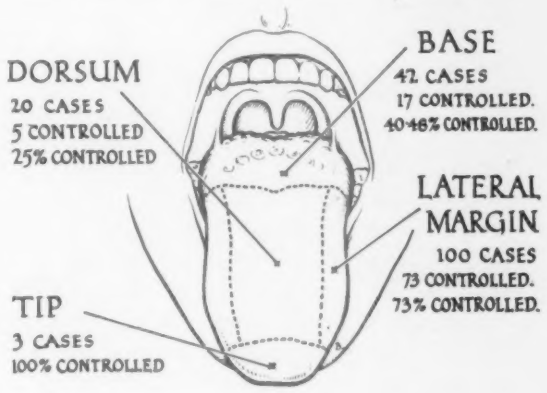
Table I

Stage	Total Cases	Males	Females
I	10	7	3
II	66	49	17
III	65	55	10
IV	26	22	4
	167	133	34
Ratio of females to males			1 to 4

CLASSIFICATION BY LOCATION

While the location of the primary lesion on the tongue is of some significance in prognosis, this is not nearly so important as is the stage of disease at which treatment is undertaken. The difference in response to treatment in different locations is, however, of some interest. Lesions arising on the posterior third of the tongue are, as a class, somewhat more radiosensitive than those originating elsewhere, but this is frequently offset by the earlier development of involvement of the deep cervical chain of lymphatics thus introducing a complication of great gravity.

The cases are arranged according to location in graphic form in Chart 1, which also shows the results of treatment in these various locations. It is seen that the commonest location has been the lateral margin, which accounted for 60 per cent of the lesions, and it is of interest to note that the left side was involved in 56 cases, the right in only 44. We have previously pointed out[2] a similar finding in cancer of the buccal mucosa where the left side was involved more frequently than the right. Since the numbers are small in both groups this observation may be merely coincidence and from the standpoint of treatment is of no particular importance.



CANCER of the TONGUE
RESULT OF TREATMENT OF PRIMARY LESIONS BY LOCATION
NUMBER OF CASES - 167.

Chart 1

PATHOLOGICAL CLASSIFICATION

In spite of the histological differences which characterize the different portions of the tongue, the vast majority of cancers which originate here fall into the group of epidermoid carcinoma or one of its subgroups. In the present series 91 per cent were classified as epidermoid carcinoma. In addition the following descriptive terms were used:

	Cases
Squamous cell carcinoma	4
Papillary epidermoid carcinoma	3
Cystic epidermoid carcinoma	1
Colloid carcinoma	1
Transitional cell carcinoma	2
Basal cell carcinoma	3

[2] In Pack and Livingston. Treatment of Cancer and Allied Diseases. Vol. 1, p. 327.

Other lesions of the tongue observed during the same period were:

	Cases
Lymphosarcoma	1
Lymphoblastoma	1
Mixed salivary tumor	1
Tuberculosis	1

INCIDENCE OF SYPHILIS

Wassermann tests were obtained in 88 cases of which 18 were positive, i.e., 20 per cent. The finding of a positive Wassermann reaction in a patient presenting an ulcerative lesion in the mouth is occasionally responsible for diverting the attention of the attending physician from the fact that the lesion is in reality a malignant one, and this may result in the loss of much valuable time if a long course of antisyphilitic treatment is undertaken. Correct diagnostic procedure should therefore invariably include biopsy as well as the Wassermann test.

METHOD OF TREATMENT

As has previously been stated, the present paper is based upon the results obtained in the treatment of approximately 200 cases of cancer of the tongue during a period of ten years, of which 167 have been analyzed. In the earlier part of this period the treatment employed included most of the recognized methods of applying radium in the form of tubes, molded applicators, moulages, needles, radon seeds, etc., and the percentage of successful results during this time conformed to the general average of 25 to 30 per cent, five year survivals.

All of the above methods are open to various objections—radium tubes because it is impossible by this means to deliver a sufficient dosage of radiation to be effective except at the risk of severe necrosis and painful reactions. The final objection, however, is that the effects are too local and treatment by this means usually fails. Radium needles and radon seeds are open to the objection that they cannot be inserted into the tongue without considerable traumatism, and it is our belief that the importance of this point has not been sufficiently emphasized. It should by now be universally recognized that in the treatment and handling of cancer *avoidance of traumatism* is as essential to a successful technique as is asepsis in general surgery. This is especially true in an organ such as the tongue, richly supplied as it is with blood vessels and lymphatics and where involvement of the regional glands introduces a complication which immediately reduces the curability of any given case at least 50 per cent.

Our efforts, therefore, have been concentrated upon developing methods in which traumatism of all kinds is avoided as completely as possible. This we regard as fundamental and the only traumatism which is permitted is the taking of a biopsy which is carried out with the greatest possible care. Rough handling of the tongue during examination under anesthesia or otherwise, the use of tongue forceps, towel clips, or sutures for retraction, frequent palpation and manipulation are all just as much to be condemned as is the rough handling of mammary cancer and should be reduced to the absolute minimum required for accurate diagnosis.

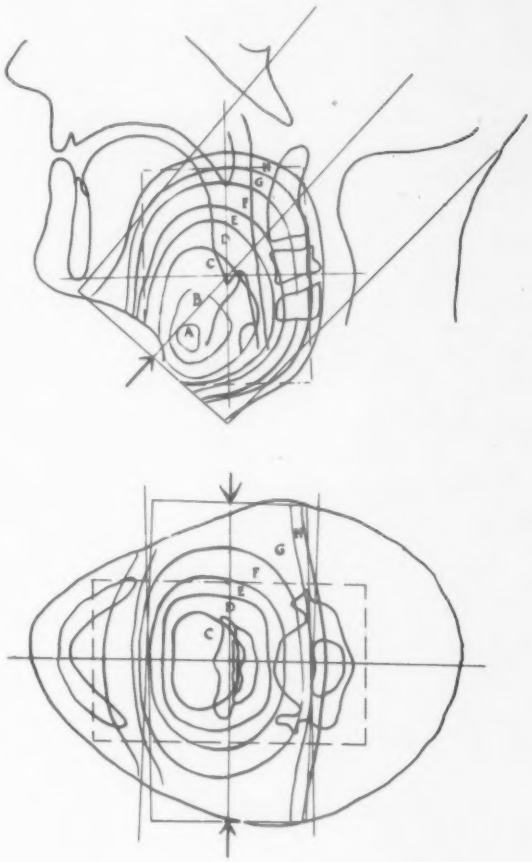
The policy which has been followed, except as qualified later, is to complete the treatment of the primary lesion before proceeding to treat secondary involvement if such is present at this time. Unless the primary lesion can be controlled, or there is reasonable evidence to indicate that it is likely to be controlled, no useful purpose is served in submitting the patient to an operative procedure as severe as a neck dissection. In general, the treatment of secondary glandular involvement has been surgical but in certain cases in which neck dissections were not considered advisable, radiation treatment of secondary involvements has been carried out concurrently with that of the primary lesion thus making possible a comparison of the effectiveness of the more radical method of surgery with that of the more conservative radiation treatment.

Treatment of Primary Lesion. Having verified the diagnosis and prepared the

mouth by careful oral hygiene including the removal of all teeth which are either septic or prevent access to the diseased portion of the tongue, treatment is commenced by external irradiation by means of roentgen rays at 400 kv. All writers on this subject have stressed the fact that cancer of the tongue belongs in the radioresistant group and a review of the literature leaves one with the impression that it is not believed to be possible to deliver sufficient radiation to the tongue by external means to control cancer without the risk of severe damage to surrounding healthy tissue. Our own experience is quite at variance with this opinion but we have found only two forms of radiation to be adequate for the purpose. These are roentgen rays at 400 kv. or the radium bomb containing 4 to 5 grams. With either of these effective control of cancer of the tongue can be secured *providing tumor doses are delivered which are in excess of 5,500 r within the entire tumor area.* By employing such doses complete control of a high percentage of lesions in any region of the tongue may be expected except those which have had their origin in the dorsum and these, with the exception of a small percentage of very early lesions, have usually been uncontrolled by any method of treatment.

Roentgen rays at this voltage appear to be somewhat more satisfactory than radium owing to the fact that they can be employed at a great distance. By making use of roentgen rays at 400 kv. at a skin-target distance of 100–110 cm. a beam of almost homogeneous radiation can be secured, the importance of which need not be stressed. The other factors employed are: a composite filter equivalent to 6 mm. Cu; half-value layer 4.5–5.0 mm. Cu, and an intensity of 7–10 r per minute. The depth dose at 10 cm. is 36 per cent.

Cancer arising on the base of the tongue is now regarded as a lesion which should be treated almost exclusively by external irradiation and may be used as an illustration. By making use of two opposed lateral portals a very even field of irradiation can be secured with a depth dose at the site of disease of 114 per cent. The skin reaction which has been adopted as our standard for this type of case is characterized by moist



Region	% of Skin Dose:	Regional Dose:
A	195 – 197	8200r to 8270r
B	190 – 195	7980r – 8200r
C	180 – 190	7560r – 7980r
D	170 – 180	7140r – 7560r
E	160 – 170	6720r – 7140r
F	140 – 160	5880r – 6720r
G	120 – 140	5040r – 5880r
H	80 – 120	3360r – 5040r
SKIN DOSE 4200r		

TUMOUR DOSE CHART
Three portals each of which receives
4200r 400 KV.

CHART II

desquamation and is secured as a rule by the administration of 3,300 r measured on the skin and including backscatter. The tumor dose from two portals each of which

has received this dosage is 3,760 r, which is inadequate.

These two lateral portals become the basis from which is derived the formula for lesions in any region of the tongue simply by the addition of other portals, depending upon the location and extent of the lesion under consideration. In the case illustrated since the tumor dose from two portals was inadequate a single direct central portal was added which also received 3,300 r, raising the percentage to 184 and resulting in a tumor dose of 6,440–6,500 r at the base of the tongue. At this dose the lesion underwent complete regression following one series of treatments without recurrence. In another similar lesion the dose necessary to cause regression required a skin dose of 4,200 r with a tumor dose of 7,980 r, but with this the lesion disappeared and healing took place without any harmful sequelae due to the treatment.

Each treatment represents a dose of 200 r delivered in forty minutes at a distance of 110 cm. (or an equivalent if teleradium is being used). Allowing for individual variations, fully established tissue reactions will be reached at total doses of 2,100–4,500 r per portal in about four weeks.

Intraoral Roentgen Therapy. When it is estimated that about half of the external dosage has been administered, the external irradiation is supplemented by intraoral irradiation, using roentgen rays at 200 kv., through an intraoral cone at 43 cm. distance. The daily dose from this source is 280 r and the full dosage is approximately 3,000 r delivered within two weeks. Thus the final tissue reaction produced in the tongue is the summation of the external and intraoral sources of radiation and *they should reach their maximum intensity simultaneously* at about the end of the fourth week. This reaction is a very intense epithelitis which is evenly distributed throughout the involved portion of the tongue and occasionally extends to other adjacent oral structures. It requires careful management but usually has subsided and healed within two or three weeks, by which time all evidence of the primary lesion in the tongue will have disappeared in all cases except the most resistant lesions. With the disappearance of the primary lesion and healing of ulceration, oral sepsis also ceases to be a serious problem and radium therapy, if required, may now be administered under much more favorable conditions. If, therefore, when the tissue reaction resulting from the external irradiation *has completely subsided* all visible and palpable evidence of the primary lesion has disappeared, no further treatment is given. If there is evidence of residual disease, radium is applied by the interstitial method using a reduced dose.

Radium Therapy. This treatment is carried out by the insertion of radium needles containing 2 mg. of radium, the filter being 0.5 mm.–0.6 mm. platinum and the dose 72 mg-hr. per cubic centimeter of tissue. It should be noted that this dose is intentionally kept low since the treatment is administered shortly after the tissue reaction from the external irradiation has subsided. It is felt that this is an extremely important point since under these conditions the radium is called upon merely to administer the "knock out" blow to those remaining cells which have already been seriously devitalized by the external irradiation. It is our opinion that roentgen therapy should invariably precede rather than follow radium therapy. In general, it is a fact that when the maximum benefit possible has been derived from roentgen therapy further benefits may be secured from interstitial applications of radium due to the more intense local effects but that this order cannot be reversed with equal advantage. Invariably, however, when this procedure is followed, the dose administered must be reduced in order to avoid necrosis.

CRITERION OF DOSAGE

In previous papers we have expressed the opinion that the criterion of dosage in all lesions open to inspection should be an observed biological reaction rather than a predetermined dose and this is nowhere of greater importance than in the treatment

of cancer of the tongue. It also will explain wide fluctuations in tumor doses delivered and skin doses which range from 1,800 to 4,500 r or even higher. The object of treatment is to secure an intense reaction throughout the entire area of involvement or, if need be, throughout the entire tongue, and the treatments must be continued until this objective has been achieved. Not infrequently it will be necessary to pass a duodenal feeding tube in order to carry the treatments to the dose required to secure proper reactions. If so this should be done and such supporting measures adopted as may be necessary for the individual case.

In spite of the production of very intense reactions accompanied by marked fibrinous exudate and resulting in extensive desquamation the treatment has been attended by comparatively little pain and up to the present no undesirable necrosis has been observed nor have there been any serious sequelae such as formerly were so common in the use of radium.

ANALYSIS OF RESULTS OF TREATMENT

Studies of the present character may be said to have two main purposes.

1. *Statistical.* To provide statistics upon which the cure rate for various forms of cancer may be established.

2. *Clinical.* To provide information in such form that an accurate clinical evaluation of the method of treatment may be reached from the standpoint of its benefit to the patient.

1. *Statistical Analysis.* The present series of cases is too small and covers too short a period of time to be of any great value for the purpose of establishing a general cure rate for cancer of the tongue. However, the influence of certain factors important to prognosis may be observed even in small numbers of cases and such an analysis shows that of 119 cases treated three years or over 37 per cent are living and free of disease, while 27 per cent are living and free of disease five years or over. Since the difference between the three and five year figures is almost exactly the expected "normal" mortality rate for this age, it would appear that in lingual cancer three year survival figures are of almost as much statistical value as five year figures.

The Influence of Involvement of the Lymph Nodes. Of the 119 cases which have been followed for three years or longer it is interesting to note that 60, or exactly 50 per cent, have never developed palpable nodes. In these obviously the result provides a measure of the degree of success obtained in dealing with the primary lesion and a measure also of the value of technical methods used. In this group in whom no palpable nodes ever developed, the three year survivals were 63.3 per cent and the five year survivals 49 per cent without recurrence to date. These figures may therefore be taken as the expected cure rate for cancer of the tongue uncomplicated by metastases to the lymph nodes. When nodes became involved the curability dropped slightly over 50 per cent, i.e. from 63.3 per cent to 27.7 per cent. All of these figures are based on older methods of treatment and both sets are lower than those now being obtained.

If it is desired to compare the results of treatment by surgical methods with those being obtained by irradiation it would be necessary to exclude all the late cases from the irradiation figures since these are "inoperable" and therefore do not appear in the surgical tables. It is doubtful if any surgical operation for cancer of the tongue has ever exceeded for skill and radical thoroughness that of Butlin, just as it is doubtful if any operation for breast cancer has ever surpassed the standard set by Halsted. Butlin's best figure for "operable" cases of cancer of the tongue was 27.9 per cent five year cures and this was accompanied by an inevitable degree of mutilation which is almost entirely avoided in the irradiation method.

It is of course obvious that the only cases which are treated entirely by irradiation are either those in whom no palpable nodes ever develop or those in whom the involve-

ment of the lymph nodes is so great as to be inoperable.

2. *Clinical Analysis.* It is suggested as the second object of the present study that an even more important question to which an answer should be obtained has to do with the actual value of treatment from the standpoint of its benefit to the patient. In other words, to what extent was the treatment successful in controlling (1) the primary lesion and (2) the secondary manifestations during the patient's lifetime regardless of whether he lived five years or not?

Previously it has been pointed out that the average age of persons suffering from lingual cancer is sixty-two years. At this age the normal life expectancy is such that only 87 out of every 100 may be expected to survive five years. Therefore from the standpoint of clinical evaluation the number surviving at the end of the five year period should be measured against the figure 87 and not 100 in order to determine the percentage of successes.*

Without laboring the point unduly, one of the cases in the present series may be used as illustration. A man aged sixty-eight was successfully treated for cancer of the tongue. The lesion healed completely without recurrence but the patient was killed in a motor accident four and one-half years later. In the purely statistical analysis he appears as a failure but so far as the patient was concerned his disease was cured as perfectly as if it had been pneumonia rather than cancer from which he had recovered. Another patient in this series was ninety-four years of age when treated. The fact that he did not survive the five year period is no reflection upon the method of treatment yet he also appears in the statistical analysis as a failure.

An additional justification for clinical evaluation based on a shorter period than the conventional five years is the opportunity it affords for critical examination of methods as a result of which any necessary changes in technique may be made. Most five year statistics are records of work done by methods already obsolete at the time of publication.

The method used for the purpose of obtaining this information for clinical evaluation has been as follows:

If following treatment the primary lesion disappeared completely, leaving no residual disease which could be detected by any method of clinical examination, and if no recurrence took place *during the patient's lifetime*, the primary lesion has been recorded as having been "controlled," provided the patient has lived two years or more following the completion of treatment. If, on the other hand, the lesion did not completely and entirely disappear or if recurrence took place at any time, the disease has been recorded as having been "uncontrolled." A similar method has been adopted in connection with secondary manifestations whether the treatment was surgical or radiation therapy or a combination of both. Cases in which for any reason the treatment was not completed have been excluded from the group, and recorded in a separate category as being inconclusive and providing no useful information for either of the above purposes.

The clinical evaluation of the results of treatment based upon the method of investigation outlined above involves the study of considerable detail which is presented for those interested. For those who merely wish the *conclusions* they are as follows:

1. *Treatment of the Primary Lesion.* The importance of early diagnosis and its influence on prognosis has been universally recognized but it is doubtful if this aspect can be overemphasized. In this series:

Of 19 cases classified as Stage I, all were "controlled," or 100%
Of 78 cases classified as Stage II, 67 were "controlled," or 78%
Of 67 cases classified as Stage III, 40 were "controlled," or 54%
Of 27 cases classified as Stage IV, 4 were "controlled," or 13%

One is impressed by the very tragic fact that all of the Stage IV cases, with a possi-

* For a more extended consideration of this aspect see Livingston and Pack's recent analytical study of the end-results of treatment of gastric cancer in which the average age is 61.2 and the analogy to lingual cancer very similar.

GENERAL SUMMARY OF TREATMENT BY STAGE OF DISEASE

Stage of Primary Lesion	Total No. of Cases	No. of Cases in Whom Treatment was Completed	Primary Lesion			
			Controlled	Per Cent	Uncontrolled	Per Cent
I	20	19	19	100	0	—
II	85	78	67	78	11	14
III	73	67	40	54	27	40
IV	30	27	4	13	23	85

Note: Percentages given are in respect to cases in whom treatment was completed.

bility of cure of 13 per cent were all at some time or other in Stage I when the possibility of cure was more than 90 per cent and that each month of delay in seeking treatment reduced this chance until cure became impossible.

These figures provide a good indication of the justification for presenting such a clinical study. The methods described were adopted during the year 1935 and each year's figures since have shown an improvement over the previous "comparable" period (Chart III). The three year survival figures for all cases is now 50 per cent as compared with the previous one of 27.7 per cent while during the year 1939 complete healing of primary lesions was obtained in 84 per cent of all cases in whom treatment was completed—a much higher figure than any previously obtained. Even if certain cases recur, as they no doubt will, encouraging progress has resulted from the change

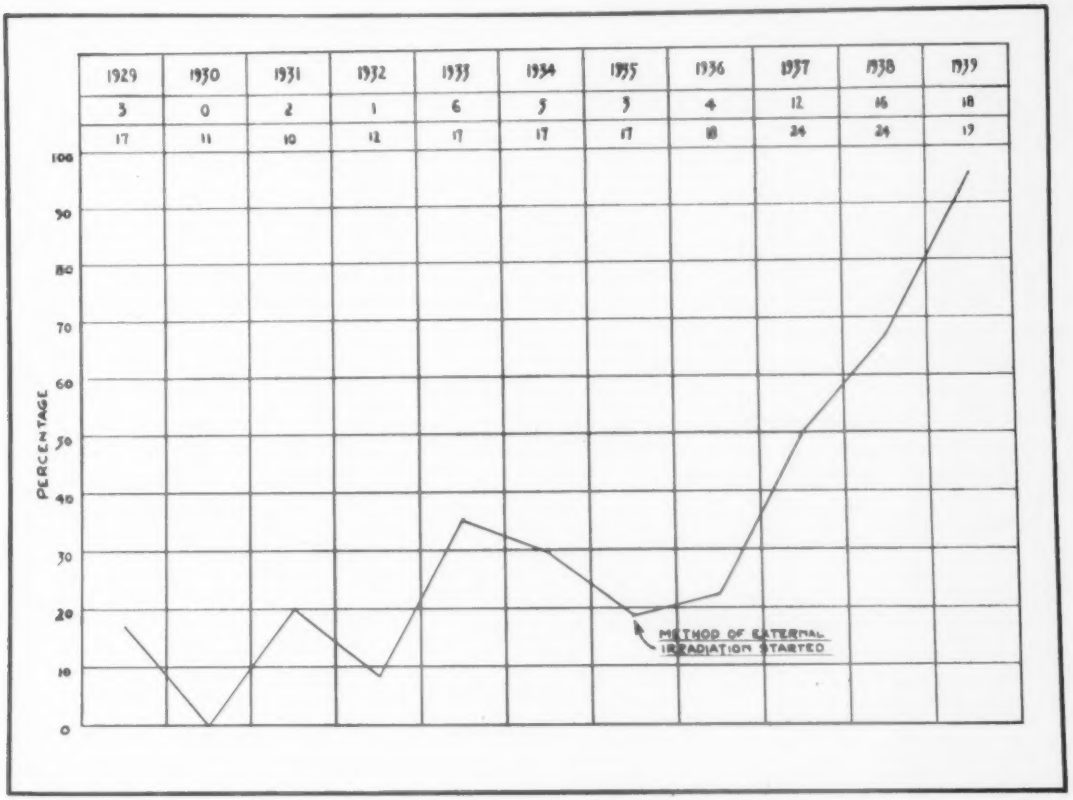


Chart III. Showing gross survival as of December, 1940.

in technique adopted. More detailed information is as follows:

STAGE I

THE PRIMARY LESION

Stage I cases treated—20—9.1% of total

Method of Treatment		Controlled	Failed	Not Completed
Radiotherapy	20	19		1

Percentage of primary lesions controlled—95%

SECONDARY INVOLVEMENT

No glands developed at any time—19—95% of total
Glands present on admission 0
Glands developed later 1

Total cases with glands 1— 5% of total

Method of Treatment		Controlled	Failed	Post-operative Mortality
Radiotherapy	1	1	0	0
Surgical	0	0	0	0
Radiotherapy and surgery	0	0	0	0
TOTAL	1	1	0	0

Percentage of secondary lesions controlled—100%

STAGE II

THE PRIMARY LESION

Stage II cases treated—85—41% of total

Method of Treatment		Controlled	Failed	Not Completed
Radiotherapy	82	65	10	7
Radiotherapy and surgery	3	2	1	

Percentage of primary lesions controlled—78.8%

SECONDARY INVOLVEMENT

No glands developed at any time—40—47% of total
Glands present on admission 22—25.9% of total
Glands developed later 23—27.1% of total

Total cases with glands 45—53% of total

Method of Treatment		Controlled	Failed	Post-operative Mortality
Radiotherapy	17	12	5	
Surgery	7	5		2
Radiotherapy and surgery	18	7	8	3
Ensol	1		1	
No treatment	2		2	
TOTAL	45	24	16	5

Percentage of secondary lesions controlled—53.3%

STAGE III

THE PRIMARY LESION

Stage III cases treated—73—35.3% of total

Method of Treatment		Controlled	Failed	Not Completed
Radiotherapy	68	38	24	6
Radiotherapy and surgery	4	2	2	
No treatment	1		1	
TOTAL	73	40	27	6

Percentage of primary lesions controlled—54.8%

SECONDARY INVOLVEMENT

No glands developed at any time—25—34.2% of total
Glands present on admission 34—46.6% of total
Glands developed later 14—19.2% of total

Total cases with glands 48—65.8% of total

Method of Treatment		Controlled	Failed	Post-operative Mortality
Radiotherapy	18	10	7	1
Surgical	10	5	2	3
Radiotherapy and surgery	19	7	10	2
No treatment	1		1	
TOTAL	48	22	20	6

Percentage of secondary lesions controlled—44.4%

STAGE IV

THE PRIMARY LESION

Stage IV cases treated—30—14.6% of total

Method of Treatment		Controlled	Failed	Not Completed
Radiotherapy	27	4	20	3
Radiotherapy and surgery	2	0	2	0
No treatment	1	0	1	0
TOTAL	30	4	23	3

Percentage of primary lesions controlled—13.3%

SECONDARY INVOLVEMENT

No glands developed at any time	5—16.6% of total
Glands present on admission	24—80% of total
Glands developed later	1— 3.4% of total
Total cases with glands	25—83.4% of total

Method of Treatment		Controlled	Failed	Post-operative Mortality
Radiotherapy	15	1	13	1
Surgery	2	0	2	
Radiotherapy and surgery	4	1	2	1
No treatment	4	0	4	
TOTAL	25	2	21	2

Percentage of secondary lesions controlled—8%

SUMMARY

1. The need for some uniform method of classifying cases of cancer of the tongue according to stage of disease is emphasized. The paper presented is based on an analysis of cases which have been thus classified in four stages. These are defined.

2. A method of treatment is described, the important features of which are absence of traumatization of the primary lesion and the greater use of external and intraoral roentgen therapy.

3. The results secured by the me hod described are considered very encouraging although three year figures only are available. These show 50 per cent of three year survivals for all cases treated as compared to 27.7 per cent for a comparable period by previous methods.

DISCUSSION

DR. GRANTLEY W. TAYLOR, Boston. It is a pleasure to be allowed to discuss Dr. Richards' paper, and to have had the manuscript beforehand in which many points were taken up which he had no opportunity to discuss this morning because of lack of time.

We are completely in agreement with him that a classification for cases of carcinoma of the tongue is a highly desirable thing and we agree, in the main, with his method of classification in regard to the extent of the disease.

We have noticed, as probably everyone else has, that those patients in whom the carcinoma has begun to infiltrate the tongue muscle, even if the extent is very small, have a very poor prognosis. The same is true of carcinoma of the breast in which the pectoral muscle is invaded. Evidently invasion of muscle favors the development of metastic disease. I feel—and I believe Dr. Richards feels—that his classification of the cases is not final but that it is very useful.

In various clinics we should have comparable groups which may be compared one with the other.

When it comes to the classification of nodes, the problem is more difficult because a clinical classification of nodes, as Dr. Richards pointed out, must be followed.

We must realize, and his last slide follows it out, that carcinoma of the tongue is a metastasizing tumor. Those in whom no metastasis takes place have been cured before it took place; but in the course of their progress they all will metastasize if they are not cured early. Classification on the basis of metastatic involvement would be desirable if clinical diagnosis were accurate. Of course, in many cases it is not, so that any plan of treatment must include the problem of what to do about the regional lymph nodes, before the plan can be called complete.

Dr. Richards went into that in his paper and you will undoubtedly recognize that it is a difficult problem and one that is not entirely solved. I noted with a good deal of interest, that although they carried out radical block resection in most of those cases in whom lymph node metastasis was present, they had a very high percentage of positive nodes in the specimens removed and very few immediately done radical operations. This suggests to me that perhaps

some of the patients may develop palpable nodes later, and might profitably have had earlier dissection. However, his cure in that group of deferred dissections was very gratifying.

Another problem is that of the patient who comes in with well advanced lymph node development still in an operable stage, and the question is whether we must wait until the subsidence of all of this tongue reaction, which in the illustrated case took two months, before anything can be done about those nodes. Another problem which is not entirely solved is that of preliminary irradiation which covers the neck area. As he showed you his portals, a good deal of radiation is delivered to the neck. We have some reluctance to carry out radical surgery in tissues which have been heavily irradiated.

In our own study of tongue carcinoma, we have found so many cases in whom the primary disease was not cured or controlled at any time, that we have rather had to defer consideration of how to manage nodes, or postpone it until such time as we could control the local disease. Dr. Richards apparently is able to control the local disease so well by his methods that perhaps we will have to solve some of these problems relating to the regional metastases a little more completely.

In an analysis of his good results, it seems to me we must recognize he has used large doses of radiation spread out over a comparatively long time and pushed to the limit of tolerance, and I think that is probably what we will always have to do if we are going to obtain satisfactory results in carcinoma of the tongue.

DR. RICHARDS (closing). It is too late for any extended reply. So far as the problem of lymph nodes is concerned, one question came up in discussion that I did not have time to refer to, which may be of some value to those of us who believe in the efficacy of the irradiation control of metastatic nodes. That is, that in all the cases operated on, biopsies were negative in just under 10 per cent and if this figure is applied as a correction factor in cases having clinically palpable nodes, but in whom biopsies are not obtained, it would make the figures presented of more value.

We think that our method of irradiation, which includes the lymph node areas at the time of treatment of the primary lesion, will reduce the incidence of secondary involvement in the neck. We think we have some information which supports this opinion but it is too early to be certain. I thank Dr. Taylor for his very kind discussion.

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THE TUMOR RESPONSE TO ROENTGEN IRRADIATION AS INFLUENCED BY THE HOST-TUMOR RELATION*

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THE problem as to how roentgen radiation cures cancer remains almost as great a mystery today as when the fact was first discovered. However, the curability of many cancers by roentgen rays and radium is now an established fact. It is equally well established that some other types of cancer cannot be successfully treated by this means. Some of the reasons for the success or failure of roentgen therapy are in part understood. Chief among these are those factors having to do with the roentgen ray per se, such as wave length, tumor dose and time intensity factors. Other factors relating to the tumor have also been established such as cell type, grade of the tumor, and its size and location. However, even when all the known factors appear to be the same there are still great variations in the response of a tumor to roentgen therapy.

A great number of investigations have been carried out to determine how roentgen radiation kills isolated cells. These investigations are of fundamental importance and the same factors may be responsible for the cure of cancer. On the other hand, it is possible that cancer may be cured in another manner since the cancer cells are destroyed and the surrounding tissue cells survive. It has been stated by some that roentgen radiation has no differential effect on the cancer cells and yet this fundamental clinical observation of the death of one cell and the survival of the other is disregarded. The experiments on which such observations are based are usually carried out in vitro. Yet it now appears that the cancer cell in vitro requires quite a different amount of roentgen radiation for a lethal effect than does the same cell in vivo. Several investigators have shown that the chemical and physical environment of the cell may determine the effect of roentgen irradiation. More recent experiments (Crabtree) have indicated that oxidation and the respiratory function of the cell are important factors in determining the effect of roentgen irradiation. Dale has also recently shown that enzymes required in the oxidative function of the cell may be profoundly affected by doses of roentgen radiation commonly employed in cancer therapy. However, the question of how roentgen radiation cures cancer is still unanswered. Attention has been directed first to the physical aspects of roentgen radiation, then to the tumor cell and more recently to the external and internal environment of the cell.

Since there was evidence that the environment of a cell in vitro, or a tumor in vivo, might determine the effect of radiation, experiments were planned in which it was attempted to vary this environment.

METHODS AND RESULTS

It was at first planned to study the effects of roentgen radiation on the same tumor when transplanted into different hosts. The tumor was a mammary cancer induced by theelin (Gardner) in A strain mice. This tumor takes and grows in 100 per cent of the A strain and invariably results in the death of the mouse. Strain A mice have a high incidence of spontaneous mammary gland cancer. This strain was crossed with C_{57} black which is a strain having a low incidence of spontaneous mammary gland cancer and the F_2 generation were inoculated with the same tumor designated as "Yale." The tumors were inoculated in the groin so as to avoid general body irradiation and the remainder of the animal screened. In all experiments a single dose of

* Read at the Twenty-sixth Annual Meeting, American Radium Society, Cleveland, Ohio, June 2–3, 1941.

roentgen radiation was given with the following factors: 90 kv., 4 ma., 23.5 cm. distance, no filtration; size of portal 2 cm. cone. The output was 149 r per minute. Proof of cure was defined as "living four months after irradiation without gross or microscopic evidence of tumor." The results are shown in Table I. It is to be noted that there is a marked difference in the curability of the same tumor in the different hosts.

TABLE I

EFFECT OF DOSE OF ROENTGEN RADIATION ON SAME TUMOR (YALE)

Host	Dose	Cure per cent
A strain	2500 r	1
A strain	5000 r	48
$AC_{57}F_2$	2500 r	82
$AC_{57}F_2$	5000 r	97

However, an objection may be raised to this experiment. It is well known that a tumor arising in a pure strain, such as the A mice, when transplanted to a hybrid may show different growth characteristics in the F_2 generation owing to segregation of tissue specificity. The tumors grew in 100 per cent of the inoculations in both strains of mice. However, in the hybrid AC_{57} there were spontaneous regressions in 28 per cent of the tumors. Sometimes these regressions occurred in two to three weeks while in others one or two months were required for complete regression. The tumors, which did not regress in the hybrids, grew progressively in a manner similar to those in the A strain. However, allowing for the regressions there was still a marked difference in the response of the tumors to roentgen irradiation in the two groups of mice. The objection might also be raised that in the second generation hybrid there would be a foreign tissue response and that even though these tumors grew as usual an additional injury such as caused by roentgen irradiation would more easily destroy the tumor. However, these objections could be overcome by using the F_1 generation in which there is no evidence of such specific tissue reaction. It has been observed (Loeb) that normal tissues grow in the F_1 generation as in the parent stock. The results of these experiments are shown in Table II. All of these tumors were irradiated with 2,500 r. For comparison the results of irradiation of another tumor (Bagg arising in the C_{57} strain) are also given.

These results indicate that the tumor-host relation determines the response of the tumor to roentgen irradiation. It should also be noted that the curability of the tumor by roentgen irradiation roughly parallels the incidence of spontaneous regression, although it is far higher. These experiments suggest that roentgen radiation augments the factor of natural resistance already present in the host.

It has been previously stated that experiments based on a transplantable tumor in hybrid animals is open to certain theoretical objections owing to the genetic constitution of the host. For this reason experiments were planned in which it was attempted to vary the constitution of the host by other means. Various investigators (Strong, Bittner) have demonstrated that the behavior of inbred strains of mice differs depending on the diet. Diet affects the life span, size and vigor of the animal, size of litters and the age at which spontaneous tumors appear as well as the number of tumors. Two diets were tested as shown in Table III. These

TABLE II

EFFECT OF HYBRIDIZATION
2500 r

Strain	Tumor	Generation	Spontaneous Regression per cent	Cures per cent
A	Yale*	Pure	0	1
AC_{57}	Yale	F_1	5	26
AC_{57}	Yale	F_2	28	82
AC_{57}	Bagg†	F_1	13	49

* Yale tumor, theelin induced in A strain.

† Bagg tumor, spontaneous breast tumor induced by forced breeding in C_{57}.

diets had been previously shown by Strong to influence the incidence of spontaneous tumors. However, no significant difference was found in the curability of tumors in these two groups of mice.

These experiments permit us to draw no general conclusions regarding diet but merely that the diet tested revealed no statistically significant difference when tumors inoculated in these mice were irradiated. Bittner and others have shown that the milk on which an animal is nursed is an important factor in determining the incidence of spontaneous breast cancer. While there

TABLE III

EFFECT OF DIET
2500 r

Diet	Host	Tumor	Roentgen-Ray Dose	No. Mice	Cure per cent
No. 1	AC_{57}-F_1	Yale	2500 r	193	27
No. 2	AC_{57}-F_1	Yale	2500 r	202	24
No. 1	AC_{57}-F_1	Bagg	2500 r	197	53
No. 2	AC_{57}-F_1	Bagg	2500 r	201	44

is no evidence that the milk factor influences the growth of a transplantable tumor yet it seemed that this might offer another method of influencing the host-tumor response to roentgen irradiation. Accordingly experiments were planned as shown in Table IV.

The results are inconclusive but indicate that the milk factor alone does not significantly alter the host-tumor response to irradiation. However, Groups III and IV in Table IV show a cure rate of 19.8 per cent and 36.4 per cent respectively in groups of 150 mice, a difference which is statistically significant. This suggests that the milk factor plus some other factor, possible genetic, may influence the constitution of the host and its response to roentgen irradiation. Further experiments are being conducted to determine this point.

TABLE IV

INFLUENCE OF MILK FACTOR

2500 r
F_1 Generation—Yale Tumor

	Host	Milk	No. Mice	Cure per cent
I	A mothers, C_{57} fathers	A milk	90	23.3
II	A mothers, C_{57} fathers	C_{57} milk	100	24.0
III	C_{57} mothers, A fathers	A milk	106	19.8
IV	C_{57} mothers, A fathers	C_{57} milk	99	36.4

SUMMARY

1. The response to roentgen irradiation of a mammary gland cancer in mice is determined by the environment in which it is growing.

2. The curability of the tumor is correlated with the presence of factors resistant to the tumor already present in the host.

3. It is suggested that roentgen irradiation augments the natural resistant factors of the host to tumor growth.

4. These experiments support the observation that the environment of the tumor cell influences its response to roentgen irradiation.*

* For discussion see page 239.

DOSAGE DETERMINATIONS WITH RADIOACTIVE ISOTOPES*†

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I. CONVERSION FORMULAE

WITH the administration of P^{32} or of similarly radioactive isotopes, beta-ray sources are directly introduced into tissue and practically all radiation emitted is utilized therein. It is therefore rather simple to calculate the dose administered once the average energy and the number of particles emitted in the tissue have been ascertained. The dose, or energy absorbed by the tissue, is merely the product of the two and this applies to all tissues and to all isotopes possessing beta-ray activity exclusively. It is tempting, indeed, to adopt a system of dosage based on some manageable energy unit (the erg or a convenient multiple) and refer clinical observations thereto.

It must be noted, however, that from a physical standpoint this form of therapy does not differ from roentgen and radium therapy, whereby β-particles are liberated in tissue by conversion of photon energy. It is therefore highly desirable to furnish the radiologist the means of determining to a first approximation, the amount of radioactive material to be prescribed in order to deliver to tissue a dose of radiation specified in terms of units already in general use.

A convenient basis of comparison for the two forms of therapy can be established by means of the energy absorbed per gram of tissue. While it is recognized that knowledge of the energy absorbed is, per se, generally insufficient to predict a given biological effect for all ionizing radiations, yet it is obvious that the existence and the importance of other factors influencing biological processes can be properly surmised and eventually evaluated only when the energy absorbed in the biological material is known with a fair degree of accuracy.

It must also be recognized at the outset that the much desired relation of equivalence between dose of radioactive isotope and tissue exposure‡ in roentgens cannot be established without specifying a substance or a tissue as a standard. It is convenient to choose air as this substance principally because tissue dosage in ordinary radiation therapy can be evaluated satisfactorily in most soft tissues by means of suitable air ionization chambers over a fairly wide range of wave lengths. The choice of a standard substance is imposed exclusively by the definition of the roentgen and by the laws governing the conversion of roentgen-ray energy into corpuscular energy. According to these laws the energy absorbed per gram of tissue when the exposure is one roentgen varies in general from tissue to tissue while for the same tissue it depends in general on the quality of the radiation.§ Proper corrections, however, can be made when the gross composition of the tissue is known and these corrections are not, in general, very large. In order then, to express the beta-ray energy absorbed in a tissue containing a radioactive isotope in numbers of the same order of magnitude as the tissue exposures expressed in roentgens, it seems expedient to adopt as a unit of energy the amount of energy absorbed by one gram of air when exposed to one roentgen of radia-

‡ The term exposure here used follows the definition in Technical Bulletin No. 1 of the Standardization Committee of the Radiological Society of North America. See *Radiology*, 1940, *35*, 138–159.

§ This aspect of radiation dosimetry has been discussed extensively in the radiological literature and is only mentioned here.

* Acknowledgment is made to the Works Projects Administration of New York City for assistance rendered under Project No. 24.
† Read at the Twenty-sixth Annual Meeting, American Radium Society, Cleveland, Ohio, June 2–3, 1941.

tion.* The *concentration* of energy represented by one of these units per gram of tissue will be referred to as the *equivalent roentgen* (e.r.).†

With these premises in mind, it is possible to express the average dose of radiation resulting from the administration of radioactive substances in equivalent roentgens by calculating the number of beta particles necessary to produce in one gram of air the same ionization produced by one roentgen of radiation.

The number N_i of ion pairs produced per gram of air per roentgen is:

$$N_i = \frac{1}{e \times \rho_a} = 1.62 \times 10^{12}$$

where e (electronic charge) $= 4.78 \times 10^{-10}$ e.s.u. ρ_a is the weight of 1 cc. of air $= 1.29 \times 10^{-3}$ grams. The energy absorbed per gram of air per roentgen (namely the energy represented by one gram-roentgen) is:

$E_r = N_i \times W_a = 5.22 \times 10^{13}$ electron-volts $= 8.3$ ergs where W_a is the energy required to produce one pair of ions $= 32.2$ volts.

It is evident then, that in order to dissipate one gram-roentgen in one gram of tissue, this gram of tissue must utilize the ionization produced by N_β β-particles such that

$$N_\beta \times \overline{V}_\beta = E_r.$$

Therefore, one equivalent roentgen requires

$$N_\beta = \frac{E_r}{\overline{V}_\beta} = \frac{5.22 \times 10^{13}}{\overline{V}_\beta} \text{ disintegrations per gram} \quad (1)$$

$\overline{V}_\beta$ being the average energy of the particle in electron-volts.

This formula is the fundamental relation of equivalence. Others more amenable to every day needs can be derived readily by taking into account the definition of the microcurie (μc.) which is the amount of radioactive material disintegrating at the rate of 3.7×10^4 atoms per second. For instance: When a whole microcurie is disintegrated, the number of particles emitted is

$$3.7 \times 10^4 \times \frac{T}{0.693}$$

where T‡ is the half life in seconds: hence one microcurie-destroyed per gram of tissue corresponds to

$$\frac{3.7 \times 10^4 \times \overline{V}_\beta \times T}{5.22 \times 10^{13} \times 0.693} = 0.88 \overline{K V}_\beta \times T \text{ e.r.} \quad (2)$$

if the average energy of disintegration is expressed in electron-kilovolts and the half life in days. It is useful also to derive a formula for the dosage rate in order to have expressions analogous to those widely used in radiation therapy. Thus the number of disintegrations per second is equal to the number of microcuries times 37.000; hence the dosage rate in equivalent roentgens per second is

$$\text{e.r./s} = \frac{3.7 \times 10^4 \times \overline{V}_\beta \times \mu\text{c/gm}}{5.22 \times 10^{13}}$$

$$= 7.1 \times 10^{-5} \overline{K V}_\beta \times \mu\text{c/gram} \quad (3)$$

Since the dosage rates obtainable with radioactive isotopes are usually small it is more convenient to express the dosage rates in equivalent roentgens per day. In this case instead of using 3.7×10^4 in formula (3) one must use the number of disintegrations per day namely:

$$\frac{3.7 \times 10^4 \times T}{0.693} (1 - e^{-.693 \times 8.64 \times 10^4 / T})$$

$$= 5.34 \times 10^4 \times T (1 - e^{-5.99 \times 10^4 / T}) \quad (4)$$

where T is the half life expressed in seconds.

Of the few radioactive isotopes suitable and available at present for therapy P^{32} is the most extensively used. It has a half life of 14.3 days[4] and it disintegrates into sulphur by the emission of beta particles of various energies ranging from 0 to 1.7

* Mayneord[1] has found it necessary to adopt the same unit (the gram-roentgen) for different purposes. The adoption of a similar unit has been found necessary also in the study of the action of neutrons on living matter.[2]

† Calculations similar to those presented in this paper have been published for the case of iodine.[3] They are, however, not given in explicit form readily applicable to other isotopes.

‡ The average life of an isotope $\overline{\text{O}} = \text{T}/0.693$ is of more theoretical significance than the half life; nevertheless, the half life is herein used because it appears explicitly in all tables listing radioactive isotopes.

million electron-volts. Its beta-ray spectrum has been determined recently with excellent accuracy by Lawson[5] and by Witcher;[6] calculations based on their results indicate that the average energy of the emitted particle is 700 electron-kilovolts (±5 per cent).* For this isotope, therefore, the formulae of equivalence are:

(a) 1 e.r ≡ 7.46×10^7 disintegrations per gram from (1)

(b) 1 microcurie-destroyed per gram of tissue ≡ 880 e.r. from (2).

The last relation can be expressed also as:

(c) 1 e.r ≡ 1.13 μc-destroyed per kg. of tissue.

Moreover, formula (4) gives $6.6 \times 10^{10} (1 - e^{-0.0485}) = 3.2 \times 10^9$ disintegrations per day hence:

$$\text{(d) } 1\ \mu\text{c. per gram} = \frac{3.2 \times 10^9}{7.46 \times 10^7}$$

$$= 42.9 \text{ e.r. per day.}$$

We may also obtain the equivalent roentgens per minute corresponding to 1 μc. per gram directly from (3) since in one minute there is no appreciable decay of P^{32}; namely

$$\text{e.r./m} = 60 \times 0.71 \times \overline{KV}_\beta \times \frac{\text{curies}}{\text{gram}}$$

$$= 0.0298 \times \mu\text{c/gram}$$

in other words, a concentration of 1 μc/gram represents a radiation intensity of only 3/100 of one equivalent roentgen per minute.

II. DOSAGE ESTIMATES ON LEUKEMIC PATIENTS

The preceding calculations have shown that the factors affecting dosage are the average energy and the number of β-particles released per unit volume of tissue. The number of disintegrations within a tissue, in turn, depends on the metabolic uptake as well as on the metabolic elimination of the isotope by the tissue itself.

Our meager knowledge of these factors precludes any determination of radiation dosage in most tissues, because it is not possible at present to determine directly the radioactivity of tissues in patients as a function of time.†

It is possible to make some estimates on radiation administered to the whole body when careful checks are kept on excreta and on radiation administered to the blood when its radioactivity is assayed at frequent intervals; these estimates, however, should be regarded merely as guides in investigating the therapeutic possibilities of radioactive isotopes and as such they are presented in Table 1 which refers to 5 leukemic patients treated by oral administration of P^{32} in fractional doses.

The theoretical body dose was obtained by multiplying the dose administered in mc/kg. by the factor 880 as indicated by formula (b). The effective body dose was calculated by multiplying the theoretical body dose by the ratio

$$\frac{\text{total mc. administered} - \text{total mc. excreted}}{\text{total mc. administered}}$$

in which the millicuries excreted were computed to the day of collection. It is recognized that this calculation is rather crude in the sense that some of the P^{32} excreted was effective in the body from the time of administration to the time of excretion and that the situation is complicated further by the fact that these patients were given fractional treatments. Nevertheless the error involved is not unduly large since the excretions thus computed represented only 15 to 30 per cent of the administered phosphorus.

More accurate results can be obtained by means of formula (d). When account is taken of the loss due to decay and to excretion, a daily estimate of the P^{32} remain-

* In order to release in tissue electrons with initial average energy equal to 700 electron-kilovolts, photons of energy $h\nu$ are required such that[7] $\sigma a/\sigma = 700$ electron-kilovolts. The result is $h\nu$-1,420 electron-kilovolts, a mean energy obtainable in practice with roentgen-ray installations operating above 2,000 kv.

† The material available at autopsy[8,9,10] is at present scanty and therefore unsuitable for quantitative interpretations on a statistical basis.

ing in the body, and hence of the number of μc. per gram effective in any one day, is available. If the latter values are plotted for the whole treatment, a curve is obtained, the area under which represents the total number of μc-days per gram of body weight. Multiplication of this number by $42.9/1-e^{-.0485}$ yields directly the number of equivalent roentgens administered.

It is unfortunate that at this stage no valid comparison can be made between the body doses thus determined and analogous doses administered in treatments of leukemic patients by means of whole body irradiation.[11] In the latter instance satisfactory computations require extensive depth dose and exit dose data which are not available at present for the conditions under which roentgen treatment was given. Rough estimates indicate that in general the energy absorbed by the body in a course of whole body roentgen therapy is likely to be about one-half the energy absorbed in the average treatment of P^{32} therapy, but the uncertainty in this figure is too large* to allow definite conclusions; furthermore, comparison as to therapeutic results would, in any case, be vitiated by the fact that whole body roentgen therapy has been used mainly as an adjunct to local therapy except in very advanced cases.

The radiation received by the blood, as shown in Table 1, was computed by graphic integration on the basis of the P^{32} concentration in samples of blood which were taken frequently during treatment.†

It is interesting to find that the apparent blood dose bears to the effective body dose a fairly constant ratio in patients of approximately the same weight and that this ratio seems to increase with the patient's weight. A possible explanation of this result is to be found in the fact that the heavier patients have a larger proportion of adipose tissue which is known to accumulate only small amounts of P^{32}. Some reservations are in order, however, on account of the small number of cases studied.

It is of some importance, moreover, to investigate the radiation dose in the main components of the blood, namely erythrocytes, leukocytes and plasma, in view of their different P^{32} uptake.[12] In order to simplify the analysis it can be assumed that

Table I

RADIATION DOSAGE IN LEUKEMIC PATIENTS

Patient	Diagnosis	Age	Body Weight	Total Millicuries Administered	Millicuries per Kilogram	Theoretical Body Dose e.r.	Effective Body Dose e.r.	Apparent Blood Dose e.r.	App. Blood Dose / Eff. Body Dose
W. Julian	Myeloid leukemia	49	77.0	17.8	.230	202	172	51.4	0.30
G. Sarah	Myeloid leukemia	28	52.2	29.8	.570	500	396	103.5	0.26
L. Isabelle	Myeloid leukemia	24	55.4	19.6	.354	312	234	61.7	0.26
K. John	Lymphatic leukemia	64	58.5	29.7	.508	457	350	85.4	0.24
J. Leslie	Myeloid leukemia	45	78.0	15.6	.200	176	153	49.4	0.32

* This is not surprising when consideration is given to the large amount of scattering taking place in roentgen treatment at 200 kv. Mayneord,[1] for instance, cannot account for nearly one-half the incident energy under conditions of treatment for which depth dose data are known very well.

† If comparison is desired between the radiation doses shown in Table 1 and the radiation doses obtained with the intravenous injections of the active deposit of Ra it must be noted that the injection of 1 mc. of the latter results in administration of 5.4 equivalent roentgens in less than four hours. This value is obtained on the assumption that all radiation from the short-lived products of disintegration is delivered to a blood volume of 5 liters.

the β-particles from P^{32} all have the same energy, that they travel in straight paths of length $R = 2{,}000\ \mu$ and that they produce uniform ionization per unit of path. If one considers the specific ionization in a corpuscle situated at the center of a sphere of radius R containing blood, it is evident that part of this ionization is produced by particles emitted by P^{32} in the corpuscle itself (internal contribution) and that the remaining part is produced by particles originating in P^{32} distributed outside the corpuscle but within the sphere of radius R (external contribution). Obviously the external contribution, I_e, is the same for all blood components and is proportional to C_b, the average P^{32} concentration in blood, namely

$$I_e = FC_b$$

where F is the number of ions produced by one β-particle. The internal contribution I_i, on the other hand, is characteristic of the corpuscle itself and can be evaluated as follows: Let C_w be the concentration of P^{32} atoms present in the corpuscle, and $\bar{p}$ the average path of the β-particle in the corpuscle. The specific ionization produced by disintegration of these atoms would be FC_w if the blood consisted of these corpuscles only. In reality only the fraction $\bar{p}/R$ of this ionization is available in the corpuscle, the rest being produced outside the corpuscle. It follows that the ratio of the internal contribution to the external contribution is:

$$\frac{I_i}{I_e} = \frac{FC_w}{FC_b}\,\frac{\bar{p}}{R} = \frac{C_w}{C_b}\,\frac{\bar{p}}{R}.$$

For a leukocyte $\dfrac{C_w}{C_b} = 10$ at most and

$$\frac{\bar{p}}{R} \simeq \frac{4}{2000} \simeq 0.002$$

hence the fraction I_i/I_e is of the order of a few per cent.

One must conclude, therefore, that since the ionization in any blood corpuscle is due mainly to the distribution of P^{32} in a much larger volume of blood, the specific ionization will be essentially the same for all corpuscles. It must be pointed out, moreover, that the radiation dosage administered to blood needs correction on account of the radiation exchange between tissues and blood in vessels of radius comparable to R. Since the peripheral blood supply forms a considerable part of the total blood volume this correction is apt to be large* and will depend, in general, on the radioactive concentration in tissues, their vascularity and their relative weight in the body. This correction will not be attempted here on account of its complexity but it must be kept in mind whenever comparative studies are made of the effect of isotope radiation on blood.†

III. SOME PHYSICAL CONSIDERATIONS ON ISOTOPE THERAPY

It is not entirely out of place to speculate somewhat on what could be done to increase the dose in a given type of tissue with respect to other tissues.

Let us assume that metabolic elimination in tissues follows an exponential law. We may then consider that in addition to radioactive decay there exists a fictitious decay characteristic of the tissue in question. Let λ_r be the fraction of isotope atoms disintegrating per unit time and let λ be the fraction of isotope atoms eliminated in the same time interval. Then if N is the number of isotope atoms present‡ per unit weight of tissue at time $t = 0$, the number of isotope atoms N_t present at any subsequent time t will be

$$N_t = Ne^{-(\lambda_r+\lambda)t}.$$

The number of atoms i_t disintegrating per unit time at any time t will then be

$$i_t = -\lambda_r N_t = -\lambda_r N e^{-(\lambda_r+\lambda)t}$$

* The author is indebted to Dr. R. S. Anderson for indicating this aspect of the problem.

† The total effect of P^{32} on blood count must, of course, take into account the very important effect of P^{32} on blood forming organs.

‡ The assumption is here implicitly made that the isotope has been deposited in tissue in time short compared to its average radioactive life and at a rate high compared to its rate of elimination.

Therefore the total number of disintegrations N_e effective in tissue from $t=0$ to $t=\infty$ is:

$$N_e=\int_0^\infty i_t dt=N\frac{\lambda_r}{\lambda_r+\lambda}. \qquad (5)$$

This expression indicates that only the fraction $\lambda_r/(\lambda_r+\lambda)$ of the atoms deposited in tissue is effective in radiation dosage. Since the radiation dose is proportional to the number of disintegrations times the average energy of disintegration $\overline{V}_\beta$ it is evident that the isotope which will deliver the highest radiation dose to a tissue is the one for which $N\overline{V}_\beta(\lambda_r)/(\lambda_r+\lambda)$ is largest and not necessarily the isotope which is taken up in the highest concentration.

To be of practical use, however, a suitable isotope should deliver radiation in limited regions or, conversely, avoid irradiating the most sensitive tissues. If one applies formula (5) to any two tissues, 1 and 2, in which the elimination rates are entirely independent, the ratio of the radiation doses D_1 and D_2 will be

$$\frac{D_1}{D_2}=\frac{Ne_1}{Ne_2}=\frac{N_1}{N_2}\frac{\lambda_r+\lambda_2}{\lambda_r+\lambda_1}$$

where N_1 and N_2 are the initial concentrations in tissues 1 and 2 and λ_1 and λ_2 their rates of elimination. This formula indicates that in order to increase the dosage ratio of tissue 1 with respect to tissue 2, an effort should be made:

(1st) to increase the ratio N_1/N_2 of the initial uptake,

(2nd) to adjust the elimination rates with respect to the decay rate. In this respect there is a limit to what can possibly be gained by reducing the elimination rate λ_1 much below the decay rate λ_2; instead, much more can be accomplished, theoretically at least, by accelerating the elimination in tissue 2($\lambda_2\to\infty$). The latter statement becomes self-evident when one considers that, in the first alternative, the usefulness of isotope retention decreases as the isotope disintegrates.

Another problem which may be of some interest concerns the dose ratio between one tissue and another tissue which utilizes the isotope in chemical compounds synthesized by the first. As in the previous case let us suppose that tissue 1 has an initial isotope concentration of N atoms per unit weight; the number of disintegrations effective in this mass will be, according to equation (5) $N_{e_1}=N\lambda_r/(\lambda_r+\lambda_1)$. Let us assume now that tissue 2 will take the isotope according to the rate $\lambda_1 Ne^{-(\lambda_r+\lambda_1)t}$ at which the tissue 1 eliminates it, and that it will lose the isotope at the rate $N_2(\lambda_2+\lambda_r)$, N_2 being the isotope concentration in tissue 2 at any time t. We must have then

$$\frac{dN_2}{dt}=\lambda_1 Ne^{-(\lambda_1+\lambda_r)t}-(\lambda_2+\lambda_r)N_2.$$

Integration of this expression gives:

$$N_2=\frac{\lambda_1}{\lambda_2-\lambda_1}Ne^{-(\lambda_1+\lambda_r)t}+Ce^{-(\lambda_1+\lambda_r)t}$$

The constant of integration C is evaluated by taking into consideration that $N_2=0$ when $t=0$, hence:

$$N_2=\frac{\lambda_1}{\lambda_2-\lambda_1}N[e^{-(\lambda_r+\lambda_1)t}-e^{-(\lambda_r+\lambda_2)t}].$$

The number of atoms i_t disintegrating per unit time in tissue 2 at any time, t, is obviously $-\lambda_r N_2$; integrating this between the limits $t=0$ and $t=\infty$ we have the total number of disintegrations N_{e_2} effective in tissue 2; namely

$$Ne_2=\int_0^\infty i_t dt=-N\frac{\lambda_r\lambda_1}{(\lambda_r-\lambda_1)(\lambda_r+\lambda_2)}.$$

The dosage ratio between the two tissues is, therefore:

$$\frac{D_1}{D_2}=\frac{Ne_1}{Ne_2}=\frac{\lambda_r+\lambda_2}{\lambda_1}.$$

This formula indicates that from a physical viewpoint, the rate of elimination of the first tissue is a more important factor in determining the dosage ratio than either the rate of elimination in the second tissue or the decay rate of the isotope.

From the foregoing examples it is clear that improvements in isotope radiation dosimetry as well as wider applications of isotope therapy are wholly dependent on quantitative knowledge of metabolic processes and on the feasibility of altering the latter to suit the desiderata of a particular type of treatment. Many of the necessary investigations in this field are at present greatly aided by the use of radioactive isotopes.

In conclusion, it is to be remembered that this form of therapy is in its infancy and that full appreciation of its possibilities and limitations cannot possibly be had at this time.

SUMMARY

Dosimetry in the treatment of malignant diseases by means of radioactive isotopes can be closely related to roentgen-ray and radium dosimetry by the use of a suitable unit of specific energy absorption.

Formulae have been derived which permit the radiologist to estimate readily the radiation delivered to tissues whenever the isotope concentration in these tissues is known. The use of these formulae is illustrated by calculations of the total body dose delivered to 5 leukemic patients who were treated by oral administration of P^{32} in fractional doses. It is evident that radiation dosage, in addition to initial isotope uptake in tissue, depends also on biological elimination. By means of elementary considerations it is shown that the importance of the latter depends partly on the half life of the isotope considered. The main difficulties encountered in isotope dosimetry are of biological nature, in the sense that the accurate determination of isotope concentration in different tissues requires either actual radioactive measurements on tissue fragments to be obtained from living patients, or calculations based on thorough quantitative knowledge of tissue metabolism, which is not available at present.*

REFERENCES

1. MAYNEORD, W. V. Energy absorption. *Brit. J. Radiol.*, 1940, *13*, 235–247.
2. GRAY, L. H. Measurement of neutron dose in biological experiments. *Nature*, 1939, *144*, 439.
3. HERTZ, S., ROBERTS, A., MEANS, J. H., and EVANS, R. D. Radioactive iodine as an indicator in thyroid physiology. II. Iodine collection by normal and hyperplastic thyroids in rabbits. *Tr. Am. Ass. Study of Goiter*, 1939. Also, *Am. J. Physiol.*, 1940, *128*, 565–576.
4. CACCIAPUOTI, B. N. Decay constant of P^{32}. *Nuovo cimento*, 1938, *15*, 213–219.
5. LAWSON, J. L. Beta ray spectra of phosphorus, sodium and cobalt. *Phys. Rev.*, 1939, *56*, 131.
6. WITCHER, C. M. Electron lens type of beta ray spectrometer. *Phys. Rev.*, 1941, *60*, 32.
7. GRAY, L. H. Radiation dosimetry. *Brit. J. Radiol.*, 1937, *10*, 721.
8. LAWRENCE, J. H., SCOTT, K. G., and TUTTLE, L. W. Studies on leukemia with the aid of radioactive phosphorus. *Internat. Clin.*, 1939, *3*, 33–58.
9. ERF, L. A., and LAWRENCE, J. H. Phosphorus metabolism in neoplastic tissue. *Proc. Soc. Exper. Biol. & Med.*, 1941, *46*, 694–695.
10. KENNEY, J. M. Radioactive phosphorus as a therapeutic agent in malignant neoplastic disease. *Cancer Research*, Feb., 1942, *2*, 130-145.
11. MEDINGER, F. G., and CRAVER, L. F. Total body irradiation with review of cases. AM. J. ROENTGENOL. & RAD. THERAPY. To be published.
12. TUTTLE, L. W., SCOTT, K. G., and LAWRENCE, J. H. Phosphorus metabolism in leukemic blood. *Proc. Soc. Exper. Biol. & Med.*, 1939, *41*, 20–25.

* For discussion see page 239.

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THE TREATMENT OF LYMPHOSARCOMA WITH RADIOACTIVE PHOSPHORUS*

A PRELIMINARY REPORT

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LYMPHOSARCOMA almost always becomes a generalized disease involving lymph nodes in widely separated areas. Except for early cases with the disease strictly localized to one surgically removable site, irradiation is, at present, the only effective means of therapy for lymphosarcoma. The ideal method of radiation treatment would be some form of systemic irradiation that would preferentially attack the scattered foci of disease. Prior to the production of radioactive isotopes by the cyclotron, such therapy could be given only by irradiation of the entire body, or by the intravenous administration of the active deposit of radon,‡ neither of which preferentially affected the disease.

Recently Medinger and Craver[2] reviewed the case histories of a large series of patients with lymphosarcoma. They noted that those patients who, shortly after the completion of their local roentgen therapy, received 50 to 75 r of whole body radiation, had a longer survival period than did patients who received only local roentgen therapy. The group of patients who had had the whole body irradiation was small but the reviewers concluded that it had probably been responsible for the longer survival period. If this therapy has increased the period of survival of these patients, the probable reason is that small, clinically non-evident foci of the disease were either attenuated or destroyed. If, then, some method of preferentially irradiating such areas by systemic therapy could be found, the damage to these areas might be greatly increased without increasing the damage to the patient as a whole.

Dr. John H. Lawrence and his associates at the University of California demonstrated that in leukemia there is a selective absorption of orally administered radioactive phosphorus by tissue infiltrated with leukemia cells,[3,4,5] a finding which has been confirmed at the Memorial Hospital.[6] If sufficient doses of this isotope are administered to humans with leukemia, the infiltrated tissues are often sufficiently irradiated by the absorbed P^{32} to bring about a remission in this disease.[3,4,6] This suggested that lymphosarcoma, with its close link to leukemia, and its usually high degree of radiosensitivity, might be effectively treated by the oral administration of radioactive phosphorus.

TRACER STUDIES

Small amounts, approximately 0.5 millicurie (mc.), of radioactive phosphorus in the form of a 1.5 per cent solution of Na_2HPO_4 were administered to a group of patients with lymphosarcoma.[6,7] Nodes were excised from these patients at intervals varying between one and thirty-one days, and in each instance the diagnosis was confirmed by microscopic examination. The node was then weighed, ashed and its radioactivity measured and corrected for decay to the date of administration of the tracer dose. The radioactivity, expressed in terms of microcuries (μc.) per kilogram of tissue, was divided by the amount of the isotope administered per kilogram of body weight,

‡ About twenty years ago, several patients with lymphosarcoma were treated by the intravenous administration of the active deposit of radon. This work was discontinued because of the excessive radiation exposure to those who prepared and administered the material.[1]

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and the result designated as the differential absorption ratio[6, 7] for that node.* This differential absorption ratio probably indicates the relative metabolic needs for phosphorus of the various tissues, since it is established by comparing the specific tissue absorption of phosphorus by the amount it would have absorbed had the phosphorus been distributed equally throughout the body. Table 1 gives the results of the tracer studies in these patients.

TABLE I

DIFFERENTIAL ABSORPTION RATIO FOR RADIOACTIVE PHOSPHORUS IN PATIENTS WITH LYMPHOSARCOMA

Case No.	Microcuries of P^{32} Administered per Kilogram of Body Weight	Days Between Administration of P^{32} and Biopsy	Differential Absorption Ratio	
			Lymph Node	Blood
N-9373	10.2	1	10.0	0.6
N-9863	9.2	2	4.6	0.5
O-1380	6.0	2	2.6	
M-8614	1.7	5	4.2	0.8
N-511	9.6	5	3.1	0.5
N-3342	5.5	6	2.4	0.3
N-9526	7.8	8	3.9	
N-1796	4.7	8	3.1	0.3
N-6776	13.3	11	2.2	
N-4354	12.6	13	4.5	0.3
N-5336	7.0	31	12.0	0.05

The two highest ratios, 10.0 and 12.0, were observed in patients biopsied on the first day and on the thirty-first day after receiving P^{32}. Exclusive of these two patients the ratio varies from 2.2 to 4.6 with a general average of about 3.0. It is to be noted that for the different patients there is a marked variation in the ratio, which apparently is neither related to the amount of P^{32} administered nor to the interval between administration and biopsy.

It is obvious that in order to irradiate lymphosarcoma tissue with P^{32} with minimum damage to normal structures, the isotope should be deposited therein in greater concentration and should be eliminated therefrom more slowly than in normal tissues. These desiderata would be represented by a high differential absorption ratio which increases with time after the administration of P^{32}. At present there is no exact knowledge of phosphorus metabolism in lymphosarcoma tissue in humans, hence at least three possibilities must be considered:

1. Lymphosarcoma with its high initial absorption of phosphorus may also have a rapid metabolic turnover, i.e. having absorbed it rapidly, excretes it rapidly; the ratio in this case would rapidly decrease with time.

2. Since this tissue has shown a greater metabolic need for the element, as shown by the higher absorption ratio, it may also retain the phosphorus at the expense of the other tissues; the ratio in this instance would increase with time.

3. The isotope may be eliminated from lymphosarcoma tissue at a rate equal to that of the entire body; in this case the ratio would remain constant with time.

Which of these situations actually exists can be determined by obtaining biopsies from an individual at different time intervals after a single dose of the isotope. This has not, as yet, been done.

Inasmuch as the absorption ratio, and possibly its relation to time, is apparently individual, it would seem best when it is proposed to treat a case of lymphosarcoma with P^{32} to administer a tracer dose of the isotope and perform a biopsy about fourteen† days later. If the ratio is good at that time, i.e. 3‡ or more, the patient, should be expected to show good therapeutic response.

This expectation is supported by the following considerations on dosage. It has

* For example: If an adult of 70 kilograms weight is given 1 millicurie (1,000 microcuries) of P^{32}, the administered dose is 14.3 microcuries per kilogram (1000/70). If in this same patient, a lymph node has absorbed 42.9 microcuries per kilogram (corrected for decay to the date of the administration of the isotope), the differential ratio of absorption is 3 (42.9/14.3).

† The ratio at this time should roughly indicate the average dosage ratio for the full period of effective irradiation from the P^{32}.

‡ It is to be emphasized that, in calculating the ratio, the measured radioactivity is corrected for decay to the date of administration of the P^{32}. This is important because the estimations of roentgen equivalent dosage always allow for the factor of decay.

been calculated that, if 1.1 microcuries of P^{32} remain in a kilogram of tissue throughout its radioactive life, 1 "roentgen equivalent" is delivered to it.[8] If an arbitrary dose of 100 microcuries per kilogram of body weight were administered, the average lymphosarcoma tissue with a differential absorption ratio of 3 would absorb 300 microcuries per kilogram, an amount which would eventually deliver a tumor dose of about 275 roentgen equivalents, if none of the isotope were excreted by that tissue. If the total administered dose over a period of weeks were 300 microcuries per kilogram of body weight, an amount which should be well tolerated by the average adult in good general condition, the tumor dose would then be about 800 roentgen equivalents. Experience with roentgen rays has demonstrated that lymphosarcoma tissue often regresses completely with tumor doses of 600 roentgens or less. It seems, therefore, that radioactive phosphorus should offer a very effective method of therapy in this disease.

THERAPY

General Considerations. The institution of any new method of therapy always raises a question of the greatest importance. What are its dangers? The only available basis for the answer to this question was the experience obtained in the treatment of leukemia with radioactive phosphorus. Thus far damage to normal tissues in patients with leukemia treated with P^{32} has not been observed in this hospital. In these patients it has been observed, however, that if the marrow is heavily infiltrated with abnormal cells, a situation which may also occur in lymphosarcoma, therapeutic amounts of the isotope often destroy the small amount of normal tissue present. It is also known that external irradiation to the marrow bearing areas frequently depresses hematopoiesis. It seemed, therefore, that the tissue most likely to be adversely affected by the isotope would be the bone marrow. If marrow aspirations are done before and during therapy it should be possible to determine whether or not this tissue was being severely damaged.

The next questions to be considered were how much of the isotope should be given at one time; how often it should be administered; and what total dose should be given. Between 100 and 120 microcuries per kilogram of body weight was selected for the initial course of therapy because, based on experience in the treatment of leukemia, it was apparently an amount that should be tolerated readily by a person with a normal bone marrow and a normal blood count. It was decided to divide this course into five or six doses given at twenty-four hour intervals for two reasons: First, a blood count can be taken when about half of this course has been administered and if there is any marked depression therapy can be stopped. Second, radioactive phosphorus must be assumed to be distributed throughout the body in the same manner as normal phosphorus and its localization in any one area should depend on that tissue's avidity for phosphorus. If small amounts of *total phosphorus** are administered, the tissue with the greatest need should take a proportionately greater amount than would be the case if large amounts were administered.[6] This division of the dose will usually keep the total amount of phosphate administered to about 90 milligrams in any twenty-four hour period, or about 10 per cent of the normal adult's daily intake of 1 gram.

It was decided that, after the completion of the first series, a period of seven to ten days should then elapse before any more of the isotope was given. This interval should be sufficient for the blood count to show any changes due to the treatment. If there is little or no change in the blood count, it should be safe to administer an additional, and similarly divided, course of from 70 to 90 microcuries of P^{32} per kilogram. This will raise the total dose to between 170 and 200 microcuries per kilogram of weight. During the administration of this second course of

* It is to be remembered that when radioactive phosphorus, P^{32}, is administered there is a much larger amount of non-radioactive phosphorus, P^{31}, administered at the same time. The ratio of atoms of P^{32} to P^{31} in the solution is about 1 to 10,000,000.

TABLE II

Case No.	N 8145 (A.L.)	K 3920 (F.S.)	N 4354 (M.C.)	N 8672 (W.K.)
Age and Sex	28 Female	50 Male	42 Female	44 Male
Past and Family History	Non-contributory	Non-contributory	Non-contributory	Non-contributory
Biopsy Diagnosis	Brill-Symmers' disease*	Lymphosarcoma	Reticulum cell lymphosarcoma	Lymphosarcoma
Date Admitted Present Illness and Course, and Treatment Prior to P^{32} Therapy	8/2/38 Enlarged nodes in groins—1 year Complete regression with 400 r roentgen rays** 6 recurrences completely regressed with similar amounts of therapy, last roentgen treatment 6/13/40	6/10/38 Enlarged nodes in several areas—3 years Complete regression with 300 r roentgen rays 2 recurrences completely regressed with similar amounts of therapy, last roentgen treatment 7/3/39	11/27/40 Enlarged nodes in neck—8 months *No roentgen therapy*	6/13/39 Mass in neck—2 years Complete regression with 300 r roentgen rays 2 recurrences completely regressed with similar amounts of therapy, last roentgen treatment 9/14/40
Date and Physical Examination at Time P^{32} Therapy Started	11/13/40 2.5 cm. nodes left groin 6 cm. abdominal mass	12/13/40 2–3 cm. nodes in left neck	12/17/40 1.0–2.5 cm. nodes both sides of neck, both axillae	3/8/41 1.0–1.5 cm. nodes both sides of neck, both axillae
Hemoglobin Red Blood Cells White Blood Cells Platelets	11/8/40 76% 3.4 M 4,800 170,000	12/20/40 80% 4.1 M 4,400 297,000	11/27/40 78% 3.8 M 8,000 300,000	12/19/40 85% 4.5 M 6,000
Marrow Smears at Start of P^{32} Therapy	Lymphocytes 69% Lymphoblasts 8%	Normal marrow	Normal marrow	Normal marrow
P^{32} Administered	11/13/40–12/9/40 6 doses totalling 9.4 mc.; (170 μc./kg.)	12/13/40–4/9/41 7 doses totalling 13.0 mc.; (240 μc./kg.)	12/17/40–3/26/41 7 doses totalling 10.7 mc.; (200 μc./kg.)	3/8/41–5/3/41 9 doses totalling 20.8 mc.; (380 μc./kg.)
Course after P^{32} Started	Complete regression of all evidence disease by 12/30/40. No recurrence to 8/1/41	Partial regression followed by increase in size of nodes and appearance of new disease	Complete regression of all evidence disease by 4/1/41. No recurrence to 8/1/41	Complete regression neck nodes; 50% regression axillary nodes. No new disease to 8/1/41
Complications Attributed to P^{32}	Marrow aplasia See text	See text	Mild, non-persisting leukopenia	None

* At the Memorial Hospital Brill-Symmers' disease, or giant follicular lymphoma, is considered to be one type of lymphosarcoma.

** Measured in air. Factors: 250 kv., 1.5 mm. Cu filter, 50 cm. distance.

TABLE II

N 6080 (G.L.)	N 7223 (N.S.)	N 8422 (S.S.)	N 3077 (G.G.)	N 8429 (F.F.)
34 Female	28 Male	38 Female	51 Male	46 Male
Non-contributory	Non-contributory	Non-contributory	Non-contributory	Non-contributory
Reticulum cell lymphosarcoma	Lymphosarcoma	Lymphocytoma†	Brill-Symmers' disease*	Lymphosarcoma
12/31/40 Enlarged nodes neck, axillae, groins—2 years. Enlarged spleen—1 month *No roentgen therapy*	3/7/41 Enlarged nodes in several areas treated elsewhere by roentgen irradiation 3 years. Enlarged nodes several areas, skin nodules—7 months 400 r to entire trunk (6 portals) caused partial regression, last roentgen treatment 4/7/41	3/14/41 Nodules in scalp—2 months. Enlarged neck nodes—1 week. Mediastinal mass (roentgen ray) 5×200 r to areas of disease yielded partial regression. New areas of disease appeared frequently, last roentgen treatment 4/10/41	5/14/40 12 lb. weight loss—3 years. Mediastinal tumor (roentgen-ray)—3 weeks. Enlarged nodes—? Complete regression of disease with 5×300 r to each area, last roentgen treatment 6/6/40	8/29/39 Enlarged nodes both groins and axilla—6 months Complete regression with 2–4×250 r, last roentgen treatment 10/31/39
1/6/41 Spleen 6 cm. below costal margin. 1.0–1.5 cm. nodes in axillae, groins and neck. Cervix infiltrated	5/5/41 Numerous 1 cm. skin nodules 1 cm. nodes in axillae, groins and neck	4/25/41 Numerous skin nodules. Enlarged cervical glands	3/28/41 Spleen 1 cm. liver 2 cm. below costal margin	12/27/40 1.0–1.5 cm. nodes in axillae and neck
12/31/40 56% 3.0 M 2,500 264,000	5/17/41 90% 5.0 M 3,700	4/24/41 55% 3.0 M 6,600 114,000	3/27/41 88% 4.5 M 9,800 160,000	12/27/40 90% 4.3 M 6,400
Lymphocytes 20% Lymphoblasts 8%	Lymphocytes 30% Lymphoblasts 8%	Lymphocytes 82% Lymphoblasts 7%	Lymphocytes 38% Lymphoblasts 8%	Lymphocytes 30%
1/6/41–4/23/41 11 doses totalling 11.2 mc.; (145 μc./kg.)	5/5/41–6/1/41 11 doses totalling 12.5 mc.; (185 μc./kg.)	4/25/41–5/16/41 11 doses totalling 12.3 mc.; (205 μc./kg.)	3/28/41–5/21/41 15 doses totalling 17.2 mc.; (260 μc./kg.)	12/27/40–4/5/41 10 doses totalling 16 mc.; (240 μc./kg.)
Complete regression all evidence disease except in cervix by 5/1/41. No new disease to 8/1/41	Good regression in all areas of disease. No new disease 8/1/41	Patient died 5/28/41 See text	Spleen not palpable, liver at costal margin. 4/23/41 No recurrence to 8/1/41	Complete regression of enlarged nodes by 4/19/41. 5/14/41 invasion and destruction of areas in ilium and lumbar spine
None	Anemia	Hemorrhagic tendency probably not due to P^{32}. See text	None	Anemia

† Clinically this patient was a case of leukosarcoma.

therapy, a complete blood count should be made, and if the white count or red count is depressed, administration of the isotope should be stopped. About ten days after the completion of the second course of therapy, a marrow aspiration should be performed and the smear compared with the one made before therapy was instituted. If there is no significant change in the marrow, and if the blood count is not significantly altered, a further treatment of between 70 and 80 microcuries per kilogram, in divided doses, can probably be safely administered. Subsequent therapy will be dependent on the effect of the previously administered P^{32} on the blood count.

The total amount that can be administered has not as yet been determined. It is probable that between 300 and 400 microcuries per kilogram will be an optimum total dose. This as previously mentioned should be tolerated by most patients with normal bone marrow and good blood counts. It would produce an approximate tumor concentration of between 900 and 1,200 microcuries (calculated as of dates of administration for each course) which should deliver a tissue dose of between 800 and 1,100 roentgen equivalents. Based on experience with roentgen therapy, such a tumor dose from P^{32} should be very efficacious in this disease if it is delivered within a reasonable period of time.

RESULTS OF THERAPY

Eighteen patients with a biopsy diagnosis of lymphosarcoma have been or are now being treated with radioactive phosphorus. In all of these patients, the isotope has been used alone and has not been supplemented by roentgen therapy unless it became apparent that P^{32} alone would not control the disease. This was done in order that a fair estimate might be obtained of the effectiveness of the isotope in causing regression of lymphosarcoma tissue. Some of these patients have had previous roentgen therapy before receiving P^{32}. In most instances the disease had recurred in the same area or arisen in a new area after the completion of the roentgen therapy. In several cases the isotope has been administered after apparent failure of roentgen irradiation to control the disease. The only criteria for selecting the cases for treatment were a proved diagnosis of lymphosarcoma, enlarged lymph nodes due apparently to lymphosarcoma, and a reasonably satisfactory blood count.

Seventeen patients are still living, the longest eight months since the commencement of therapy. Five patients have had complete regression of the enlarged nodes and have remained free from recurrence of the disease for periods of time varying between one and eight months. In one patient there has been complete regression of enlarged neck nodes, and more than 50 per cent regression of enlarged axillary nodes. One patient had good regression of all enlarged lymph nodes but shortly after the administration of the isotope was stopped, he had evidence of bone involvement, which was proved by roentgenograms. In one case the nodes not only failed to regress, but actually increased in size during the period of administration of the radioactive phosphorus. One patient died one month after the commencement of therapy. The remaining 9 patients have been placed on radioactive phosphorus therapy too recently to be considered at this time. The method of treatment outlined in the previous section was not used in the earlier cases, but was developed and has been used in the treatment of the last 12 cases.

Table II presents a résumé of the history and treatment of the 9 patients in whom it is believed that an evaluation of the immediate therapeutic results is possible.

Regression of the diseased nodes in Case N-8145 was prompt and complete and there has been no recurrence in the eight months since the cessation of therapy, the longest period of freedom from disease this patient has had. Unfortunately a serious complication occurred in the form of marrow aplasia. It is to be noted that prior to the institution of the therapy, this patient's marrow was

markedly infiltrated by lymphocytes. Patients with Brill-Symmers' disease (giant follicle lymphoma), in whom such marrow infiltration occurs, often die with marrow aplasia. It is open to question, therefore, whether the marrow aplasia in this case was caused by therapy or whether it was a coincidental happening and a part of the natural course of disease. It may have been due to both factors. Of greatest importance, however, is the fact that there is now apparently a beginning of recovery of the marrow. If this recovery continues and it returns to normal without the previous lymphocytic infiltration, a great deal will have been accomplished by the therapy. At present, this patient's hemoglobin is maintained at a level of about 60 per cent by administering a transfusion every two or three weeks.

Case K-3920 represents a complete failure of radioactive phosphorus therapy. It cannot be said in explanation that the disease was not radiosensitive because small doses of roentgen rays, about 300 r, caused good regression in the areas of disease which appeared in the course of P^{32} therapy. The differential absorption ratio for lymphosarcoma tissue in this patient was 2.2 after eleven days, indicative of a fair retention of the isotope. A biopsy taken during therapy and two hours after a dose of the isotope had a concentration of 231 microcuries per kilogram, an amount which would deliver 10 r to the tissue in a twenty-four hour period. From these two factors it seems safe to assume that this patient did deposit P^{32} in lymphosarcoma tissue and, retain it there for eleven days in fairly good concentration. The explanation of P^{32} therapy failure in this case may rest in the time factor. It would seem that the disease was hyperactive in its growth rate and that the radiation was delivered by the isotope too slowly to control it. In other words, the growth rate of the disease exceeded the "cancericidal" rate of radiation of the P^{32}. This belief is supported by the patient's clinical course after the administration of the isotope was stopped and roentgen therapy instituted. New lesions appeared almost at weekly intervals, and not infrequently they recurred in an area that had had roentgen therapy only a short time previously.

In Case N-4354 there was disappearance of all evidence of disease despite a somewhat irregularly administered therapy. The fall in the white count was not serious and with the cessation of therapy the leukocyte count began to rise. This patient has now been clinically free of disease for four months.

Case N-8672 received a moderately large dose of P^{32} with complete control of the disease in one area and nearly complete control in another area. Additional therapy may destroy the residual disease. There has been no depressive effect on hematopoiesis. On May 2, 1941, an axillary node was excised, its radioactivity measured and a section examined microscopically. No cytological changes were noted. The radioactivity of the node, as of the day of removal, was 163 microcuries per kilogram, a concentration which would deliver to that tissue 7 r in a twenty-four hour period.

Case N-6080 was treated cautiously because of the patient's low white count. There has been excellent regression of the disease and marked improvement in the patient's general condition. The marrow smears have shown a slight increase in myelocytic elements but otherwise were unaltered by the therapy. On February 3, 1941, a lymph node was excised for pathological examination. No changes attributable to the therapy were seen. The radioactivity of this tissue, as of the day when removed, was 130 microcuries per kilogram, an amount which would deliver 6 r to the tissue in twenty-four hours. As the total dose of P^{32} prior to removal was only 2.7 mc. (40 microcuries per kilogram of weight), and the last dose was given eighteen days before the biopsy, this is an extremely high concentration of the isotope. It indicates a high differential absorption ratio and good retention of the isotope, which is probably the reason that this pa-

tient had such a prompt and excellent response to P^{32}.

Case N-7223 is of special interest because roentgen therapy controlled the disease only partially, whereas the administration of P^{32} a few weeks later brought it apparently under complete control. This patient had widespread disease with numerous skin nodules and enlarged lymph nodes. High voltage roentgen radiation, 2×200 r, was administered to each of six large portals, with about 50 per cent regression of disease in the treated areas. Four weeks later administration of P^{32} was started and from May 15, 1941, to June 23, 1941, fifteen doses totaling 235 microcuries per kilogram were administered. On July 10, 1941, there was almost complete regression of all evidence of disease. This patient now has a moderate secondary anemia, but in view of the therapy required to control the disease this is not surprising.

In Case 62702 the patient died one month after the institution of P^{32} therapy. This case was clinically a leukosarcoma, a type that responds poorly, if at all, to roentgen irradiation. In this instance roentgen therapy administered prior to the P^{32} was ineffectual. The lesions are frequently radioresistant; they grow rapidly and new ones are constantly appearing. The hemorrhagic diathesis was not related to the P^{32} therapy, because it manifested itself before any of the isotope was administered. This case is a failure of radioactive phosphorus therapy in a type of lymphosarcoma in which other forms of radiation therapy are also usually ineffectual.

Case N-8429 had a good initial response to the P^{32} therapy with practically complete regression of all evidence of disease. Six weeks after the cessation of administration of the isotope, roentgenograms revealed a destructive process in the ilium. Four weeks later a lesion was discovered in the lumbar vertebrae and at the same time enlarged nodes were palpated in the patient's neck. Roentgen therapy was used to control these lesions because the patient had a moderate secondary anemia and it was not believed wise to administer more of the isotope.

DISCUSSION

It is not proposed that radioactive phosphorus completely replace roentgen radiation in the treatment of lymphosarcoma. Patients with a moderate amount of disease, enlarged nodes in several areas but no bulky masses, who have had no previous radiation therapy are probably the best cases for P^{32} therapy. Patients who have large masses of lymphosarcoma tissue, particularly if they interfere with some normal function, should probably have these areas treated by roentgen irradiation. The administration of the isotope in this latter instance would be for the purpose of destroying the smaller, or clinically non-evident foci of disease. When both roentgen radiation and radioactive phosphorus are used, either the administration of the isotope should be postponed until the completion of the roentgen therapy or the amount administered in each course should be less than that usually given. When the field of irradiation includes marrow bearing areas such as vertebrae or sternum, the use of radioactive phosphorus should be postponed until roentgen therapy in these areas is completed. Then if the blood count has not been materially affected, cautious administration of the isotope may be started.

This combination of radioactive phosphorus and local roentgen irradiation may prove to be the type of therapy most successful in the treatment of lymphosarcoma. It provides strong local radiation therapy to readily recognizable areas of disease, and also diffuse systemic irradiation to latent and unsuspected areas of disease. By proper use of this combination, it may be possible to prolong the survival period of these patients.

It is to be emphasized that frequent blood counts are necessary during all phases of the therapy. Marrow aspirations should be done before and at least twice during treatment. A marked and persisting depres-

sion of red cell count, white cell count, or platelet count, or evidence of damage to marrow cells, is a positive warning for cessation of therapy. Reinstitution of therapy after disappearance of these changes should be done cautiously. While some depression of the blood count is to be expected, the point at which this becomes serious and an indication for cessation of therapy is a matter of judgment based on the observer's experience. However, if the leukocyte count falls below 3,500, if the platelet count falls below 150,000, or if the red cell count is decreased by more than 15 per cent of its original value, it is probably best to stop the administration of P^{32} until the blood count has returned to nearly its original level.

Serious damage to the hematopoietic system has been noted in only one instance, Case N-8145. In this particular case there was marked lymphocytic infiltration, about 70 per cent, of the bone marrow at the time therapy was started. This is not an uncommon finding in lymphosarcoma and Brill-Symmers' disease and is usually a prelude to a downhill course marked by anemia and leukopenia. It is quite possible that the radiation administered to the marrow by the absorbed phosphorus hastened its degeneration and the appearance of the anemia. However, this patient is still living (eight months after the cessation of therapy) and the bone marrow is apparently regenerating. In 2 patients (N-7223 and N-8429) there has been a somewhat marked depression of the blood count. In several patients there has been a temporary depression of the leukocyte count and platelet count which has not reached a serious point at any time. It would seem that unless the marrow shows damage before therapy is started, the patients will probably tolerate an adequate therapeutic amount of the isotope. Until many more patients have been treated and more time has elapsed, it will not be possible to evaluate further the dangers of this therapy.

Six patients have had lymphosarcoma tissue removed at varying times during therapy to determine if any cytologic changes attributable to the P^{32} could be detected. The nodes have been carefully examined by Dr. Stewart and his associates in the Department of Pathology and compared with biopsies made before the institution of therapy. No definite cytological changes attributable to the isotope have been noted.

SUMMARY AND CONCLUSIONS

Tracer doses of radioactive phosphorus were administered to a group of patients with lymphosarcoma. From one to thirty-one days later a lymph node was excised from each patient and, after suitable preparation, its radioactivity measured and corrected for decay to the date of administration of the P^{32}. It was found that the average lymph node invaded by lymphosarcoma had a differential absorption ratio of about 3. Application of suitable formulae for estimating the amount of radiation that might be delivered to such tissue indicated that P^{32} might be a useful therapeutic agent in this disease.

A method of therapy, based in part on previous experiences in the treatment of leukemia, has been described. Courses of 70 to 100 microcuries of P^{32} per kilogram of body weight are administered in divided doses at intervals of from seven to fourteen days.

Eighteen patients with lymphosarcoma have been or are now being treated with radioactive phosphorus. Five patients have had complete regression of all evidence of disease and have been free of recurrence for from one to eight months. One patient had complete regression in one area and more than 50 per cent regression in the other area of disease. One patient had a good initial regression followed by rapid recurrence of disease. One patient did not respond to the therapy and one patient died during therapy. The remaining nine patients are still under treatment. These results seem to indicate that radioactive

phosphorus is a useful and effective method of therapy in lymphosarcoma.

Careful consideration of the potential dangers of radioactive phosphorus therapy led to the conclusion that the tissue most liable to early and serious damage was bone marrow. This damage should be preventable if frequent blood counts are made, and if several marrow aspirations are performed and compared during the course of administration of the isotope. Serious damage to this tissue has been observed in only one case. In that case there was marked infiltration of the bone marrow by lymphocytes before P^{32} was administered. In two cases moderate anemia followed the administration of the isotope, but with cessation of therapy the blood picture has improved.*

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* For discussion see page 239.

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REFERENCES

1. DUFFY, J. J. Personal communication.
2. MEDINGER, F. G., and CRAVER, L. F. Total body irradiation with review of cases. AM. J. ROENTGENOL. & RAD. THERAPY, to be published.
3. LAWRENCE, J. H., SCOTT, K. G., and TUTTLE, L. W. Studies on leukemia with the aid of radioactive phosphorus. *Internat. Clin.*, 1939, *3*, 33–58.
4. LAWRENCE, J. H. Nuclear physics and therapy; preliminary report on a new method in the treatment of leukemia and polycythemia. *Radiology*, 1940, *35*, 51–60.
5. TUTTLE, L. W., SCOTT, K. G., and LAWRENCE, J. H. Phosphorus metabolism in leukemia blood. *Proc. Soc. Exper. Biol. & Med.*, 1941, *41*, 20–25.
6. KENNEY, J. M. Radioactive phosphorus as a therapeutic agent in malignant neoplastic disease. *Cancer Research*, Feb., 1942, *2*, 130–145.
7. KENNEY, J. M., MARINELLI, L. D., and WOODARD, H. Q. Tracer studies with radioactive phosphorus in malignant neoplastic disease. *Radiology*, 1941, *37*, 683–690.
8. MARINELLI, L. D. Dosage determinations with radioactive isotopes. AM. J. ROENTGENOL. & RAD. THERAPY, Feb. 1942, *47*, 210–216.

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THE RELATION OF PHOSPHATASE ACTIVITY IN BONE TUMORS TO THE DEPOSITION OF RADIOACTIVE PHOSPHORUS*

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INTRODUCTION

MOST of the experimental work on radioactive phosphorus at Memorial Hospital has been undertaken primarily for the purpose of determining whether this isotope would localize in malignant tumor tissue in sufficiently high concentration to be of therapeutic value. The results of determinations of radioactive phosphorus in the tissues of patients to whom this material had been administered have also yielded considerable information on the metabolism of tumors, especially those of bone, and these findings form the subject of the present paper.

The work of numerous previous investigators has brought out the principal factors which influence the storage of radioactive phosphorus.[5] Since all tissues contain phosphorus, and since the radioactive isotope is chemically indistinguishable from the normal one, all tissues have the capacity to store radioactive phosphorus to some extent. Normal adult tissue uses phosphorus to replace that lost in catabolism. Such tissues will take up any radioactive phosphorus which is available at a rate which depends on the metabolic rate of the tissue and on its total phosphorus content. Thus, muscle takes up radioactive phosphorus rapidly because of its high metabolic rate, but the absolute concentration attained is never high because of the low total phosphorus content and rapid turnover. On the other hand, bone stores radioactive phosphorus slowly because of its low metabolic activity, but it will ultimately fix a large proportion of the supply available in the body because of its extremely high phosphorus content. Growing tissue takes up radioactive phosphorus more rapidly than the corresponding adult tissue because it is forming new substance as well as replacing old. If the radioactive phosphorus is available in high concentration for only a short period of time, the isotope deposited in the growing area will later be diluted by the large amounts of normal phosphorus subsequently laid down. This process of dilution may not be marked until the activity of the isotope has been considerably reduced by decay. Thus the radiation dose per gram of growing tissue will in general be higher than that per gram of adult tissue of similar type. Certain organs, such as the liver, serve as depots for the temporary storage of phospholipids and other phosphorus rich compounds. Both the initial uptake and subsequent loss of radiophosphorus in these organs is usually rather rapid.[4]

Normal bone produces an enzyme, alkaline phosphatase, which splits organic phosphorus compounds to produce a local excess of inorganic phosphate radicals for deposition as calcium phosphate. Extracts of normal bone also contain extremely small amounts of acid phosphatase, but this probably originates in non-osseous elements. Many tissues other than bone produce acid or alkaline phosphatase or both. The amounts are usually small, and the alkaline phosphatases commonly lack the sharp peak at pH 9.4 characteristic of bone phosphatase. The function of these non-osseous phosphatases is not well understood.

Growing bone contains ten or more times as much phosphatase as the corresponding adult bone, and the phosphatase activity

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affords a good index of the rate of growth. Some bone tumors contain little or no alkaline phosphatase, and apparently lack the capacity to lay down calcium phosphate. The majority of osteogenic sarcomas, however, contain large amounts of alkaline phosphatase. The phosphatase activity tends to be higher the more osteoplastic the tumor is and the more rapidly it grows, although the relationship is not a quantitative one.[11] Many of the metastases from high phosphatase bone tumors contain large amounts of phosphatase, and some of these metastases lay down calcium phosphate. Since high phosphatase bone tumors grow rapidly and have a high phosphorus content, they should theoretically fix more radioactive phosphorus than any other tissue except perhaps the epiphyseal region of young bone. This should also be true of the metastases which form bone.

In considering the probable usefulness of radioactive phosphorus in the treatment of various types of tumor, the radiosensitivity of the tumor must be considered in addition to its capacity to fix phosphorus. Thus, it has been shown by one of us[6] that both carcinoma of the breast and leukemic nodes take up two to four times as much of the isotope as analogous normal organs. This is probably due to the higher metabolic activity of the malignant tissue, and is in no way a specific property of the malignant state. Carcinoma of the breast is moderately radioresistant, so that it is not possible to administer enough radiation by means of radioactive phosphorus to inactivate the tumor without doing serious damage to the organism as a whole. On the other hand, leukemic tissue is so radiosensitive that radioactive phosphorus has proved to be a very useful agent in the treatment of leukemia. Among the bone tumors, endothelioma grows rapidly, but usually does not mineralize. We should therefore expect it to take up somewhat more radioactive phosphorus than normal tissue by virtue of its rapid growth, but the excess is not likely to be large because calcium phosphate is not laid down. The radiation from a moderate amount of isotope might well be of therapeutic significance, however, because the tumor is rather radiosensitive. In contrast to endothelioma of bone, osteogenic sarcomas are almost universally radioresistant, a dose of at least 4,000 r to the tissue usually being required to cause even temporary inactivation.[11] A few osteogenic sarcomas produce no alkaline phosphatase and do not mineralize. Radioactive phosphorus cannot be expected to deposit in these tumors in sufficient concentration to affect their activity significantly. The majority of osteogenic sarcomas have a high phosphatase activity and have the capacity to form new bone. As explained above, these tumors may be expected to fix radioactive phosphorus in high concentration. While it would probably be dangerous to the health of the patient to attempt to administer sufficient radioactive phosphorus to inactivate these radioresistant tumors by radiation from this source alone, yet the use of radioactive phosphorus in conjunction with external roentgen therapy might well give good results.

It has been shown by one of us elsewhere[11] that the presence of a normal serum phosphatase in a patient with a bone tumor does not necessarily mean that the tumor is not a phosphatase producer, but that an elevation in the serum phosphatase of a bone tumor patient with normal liver function indicates that the tumor contains abundant phosphatase. Thus, determination of the serum phosphatase may be used to decide whether or not a patient is likely to benefit from radioactive phosphorus treatment.

In the care of most bone tumors radical surgery has been and remains the treatment of choice,[2] so that it is only in the comparatively small group of cases where the lesion is inoperable when first seen or where the patient refused operation that radiation therapy must be used as the sole agent in the attempt to control the primary tumor. The main problem is usually the prevention of metastases, and in this field radioactive phosphorus seems likely to prove useful.

The fact that each type of tumor tends to metastasize to only one or two structures in the body suggests that minute tumor emboli are much more sensitive to unfavorable influences than is the primary lesion, and that they only become established in areas where the environment is favorable. If these small fragments possess the capacity to fix radioactive phosphorus, then the damage which they receive from radiation may devitalize them sufficiently so that they will succumb to environmental influences.

METHODS

The radioactive phosphorus as a 1.5 to 3.0 per cent solution of Na_2HPO_4 with an activity of 200 to 500 microcuries (μc.) per cubic centimeter was supplied to us through the courtesy of Dr. John H. Lawrence of the University of California. It was administered by mouth, or in two cases by vein, in single or repeated doses. At intervals varying from seventeen hours to three months thereafter tissue was obtained at operation or autopsy. Different types of normal and pathological tissue were freed by careful dissection, and where various portions of a tumor appeared to differ widely in metabolic state, these were handled separately. The tissue was finely divided with scissors or rongeur, a part of the resulting hash was dried for radioactivity and total phosphorus measurements, and the remainder extracted for phosphatase determination. All calculations were made on the basis of wet weight.

After drying, the samples for radioactive phosphorus determination were ashed in a muffle furnace and the radioactivity was measured with a Geiger counter. All readings were corrected for decay. Where single doses were given the corrections were made to the date of administration; when the doses were multiple, the corrections were made to the date of removal of tissue. Tissue doses were calculated in equivalent roentgens by the method of Marinelli.[7]

The total phosphorus of the ash was then determined by a modification[8] of the methods of Pregl and Roth[9] and of Scott.[10] Alkaline serum phosphatase was determined at pH 9.1 electrometric) by the method of Bodansky[1] as modified by Woodard, Twombly and Coley.[12] The method for tissue phosphatase was based on that of Franseen and McLean[3] but with numerous changes. Acid tissue phosphatase readings were made at a pH between 4.0 and 5.0 and the alkaline at pH 9.1. One-half per cent sodium β-glycerophosphate with or without veronal buffer was used as substrate. Activities were expressed as Bodansky units per gram of tissue.

RESULTS

The results are summarized in the accompanying tables. The radioactive phosphorus content of the various tissues is expressed by means of the "differential absorption ratio." This ratio is obtained as follows: From the total amount of radioactive phosphorus administered, the amount excreted is subtracted. In the cases where excretion studies were not made, an average excretion of 20 per cent is assumed to have taken place. The remaining 80 per cent of the administered dose is termed the "retained body dose." This is then divided by the weight of the patient to give the retained dose per kilogram of body weight. The radioactive phosphorus concentration per kilogram of the different tissue specimens is then divided by the average retained dose per kilogram of the whole body to give the differential absorption ratio. A ratio greater than unity indicates that the tissue under examination takes up more than its proportional share of the radioactive phosphorus present in the body as a whole.

The use of this method of expressing the radioactive phosphorus concentration permits of a comparison between patients who had received different doses as well as between different tissues in the same patient.

The last column in the tables is headed "differential isotope ratio." This is obtained by dividing the differential absorption ratio by the number of grams of total

phosphorus in each kilogram of the tissue under examination. The resultant figure is a function of the extent to which, in the particular specimen, normal phosphorus has been replaced by the radioactive phosphorus present in the whole body. It must be emphasized that the figure does not represent the ratio of the number of atoms of the two isotopes present.

The radioactive phosphorus content is shown on a number of specimens of normal tissue on which no phosphatase determinations were made. This is because the usual phosphatase activity of normal tissues of these types is known from previous work. Thus, shaft of adult long bone contains minimal amounts of acid phosphatase and 0.1 unit per gram or less of alkaline phosphatase (Cases II, III, VI and XIV); corresponding bones in children contain up to 0.5 unit per gram (Cases V and VIII). Of the patients shown here, only Cases V, VII, VIII, IX, X and XV were growing rapidly enough to raise the phosphatase activity of long bone or serum. Extracts of normal muscle have barely perceptible glycerophosphatase activities (Case IV). Muscle does, of course, possess enzymes capable of breaking down the phosphorylated intermediate products of carbohydrate metabolism, but these do not act on β-glycerophosphate under the conditions of the present work. Extracts of normal liver and kidney contain 0.5 to 1.5 units per gram of acid glycerophosphatase and 0.5 to 1.0 units per gram of alkaline glycerophosphatase (Case XI). The alkaline phosphatase of these organs lacks the sharp peak of activity at pH 9.3 to 9.4 which characterizes bone phosphatase.

The majority of the patients included in the tables received "tracer" doses of radioactive phosphorus, that is, single doses administered for experimental purposes. The amounts given were usually 0.5 millicurie (mc.) or less, although 3 patients (Cases II, VI and XV) received somewhat more. Three patients (Cases VII, VIII and IX) were given repeated doses over periods of several weeks for therapy or prophylaxis.

The results for patients with osteogenic sarcoma are shown in Table 1.* For the first 6 cases the time which elapsed between the administration of radioactive phosphorus and amputation was short, and the phosphatase activity of the tissues at the time of examination was essentially the same as that which existed during the whole period when the isotope was available. These cases will therefore, be considered first.

Case 1, J. C., a well developed youth of sixteen, had a large osteogenic sarcoma of the lower end of the right femur. The tumor had been treated by roentgen irradiation at another institution with some temporary inhibition of growth, but was fully reactivated by the time he presented himself at Memorial Hospital. His serum phosphatase was somewhat elevated at 9.0 units per 100 cc., a postoperative reading showing that his normal level was about 5.5 units. He received 0.466 mc. radioactive phosphorus intravenously, and amputation was performed seventeen hours later. The tumor on gross examination was markedly inhomogeneous, so three separate specimens were taken for analysis. The location of these specimens is shown in Figure 1. It is seen that there was a wide range of alkaline phosphatase activity in the different portions of the tumor. Even in as short a time as seventeen hours this difference is reflected both in the absolute amount of radioactive phosphorus deposited and also in the amount of P^{32} relative to P^{31}. This is also true for the normal bone, for which the alkaline phosphatase may be assumed to be 0.1 to 0.2 unit per gram as explained above.

The great difference in the phosphatase readings on different portions of this large tumor throws some light on the confusion which has existed in the literature regarding the relation between phosphatase and osteoplasia. While it is true in general that the more sclerosing a tumor, the higher its phosphatase content is likely to be, one of

* All the patients in Table 1 and Case XV in Table II were from the Bone Tumor Service of Memorial Hospital. We wish to express our thanks to Dr. B. L. Coley for permission to use these cases.

TABLE I

OSTEOGENIC SARCOMA

Case No.	Diagnosis	Age and Sex	Serum Phosphatase Units per 100 cc.	Dose P^{32} mc.	Time after P^{32}	Tissue	Tissue Phosphatase		Differential Absorption Ratio	Differential Isotope Ratio
							Acid	Alkaline		
							Units per gram			
I	Osteogenic sarcoma, right femur	M 16	9.0	0.47	17 hrs.	Tumor A	0.25	34.7	5.8	0.79
						Tumor B	0.07	2.8	1.7	0.43
						Tumor C	0.02	0.32	1.1	0.018
						Normal femur shaft			0.7	0.0072
						Normal tibia shaft			0.6	0.0068
						Normal muscle			0.7	0.53
						Normal red marrow			1.1	
II	Low grade osteochondrosarcoma, left femur	M 31	19.8	2.0	38 hrs.	Tumor	0.15	25.0	7.2	2.7
						Normal femur shaft	0.01	0.01	2.1	0.017
						Normal muscle			0.9	
						Normal yellow marrow			0.3	
III	Osteogenic sarcoma, left fibula	F 54	11.5	0.55	52 hrs.	Tumor A	0.20	1.6	0.6	0.97
						Tumor B	0.25	40.0	1.0	1.3
						Tumor C	0.84	115.0	4.6	
						Normal femur shaft	0.06	0.09	0.4	0.0051
						Normal muscle			0.7	
IV	Osteogenic sarcoma, left tibia	F 16	15.5	0.09	3 days	Cancellous portion tibia	0.08	1.6	3.1	
						Epiphysis normal fibula	0.02	0.30	1.5	
						Shaft normal fibula	0	0.01	0.8	
						Normal muscle	0.01	0	1.9	
V	Osteogenic sarcoma, left femur	M 13	10.3	0.50	6 days	Periphery main tumor	0.10	0.82	8.3	
						Center, main tumor	0.05	0.34	2.4	
						Tumor in shaft	0.09	0.68	4.0	
						Shaft normal fibula	0.02	0.20	1.7	
						Normal muscle			0.9	
						Normal red marrow			1.5	
VI	Osteogenic sarcoma, right femur	M 17	6.4	2.5	7 days	Tumor		0.18	2.6	
						Normal fibula shaft		0.01	0.4	
						Normal fibula epiphysis		0.15	0.7	
						Irradiated femur epiphysis		0.10	0.4	
						Normal muscle			0.2	
VII	Osteogenic sarcoma, right femur	M 14	12.0 before P^{32}	10.7	28 to 4 days	Tumor, partly sclerosing	0.06	0.20	1.8	0.10
						Tumor, hemorrhagic	0.14	0.20	4.3	0.13
						Irradiated femur epiphysis	0.02	0.06	1.0	0.030
						Normal femur shaft			0.9	0.0096
						Normal muscle			0.7	0.43
VIII	Large spindle cell and giant cell osteogenic sarcoma, left humerus	M 16	11.0 before P^{32} 5.5 after P^{32}	10.9	34 to 5 days	Hemorrhagic tumor A	0.06	0.33	0.45	0.87
						Calcified tumor B	0.13	2.0	3.8	0.051
						Shaft normal radius	0.03	0.50	2.0	0.021
						Epiphysis normal radius	0.06	0.67	3.0	0.067
						Normal muscle			0.7	0.40
IX	Osteogenic sarcoma, left femur	F 14	5.1 before P^{32} 5.8 after P^{32}	19.0	165 to 66 days	Primary tumor from marrow cavity	0.02	0.62	0.1	0.0025
						Primary tumor, subperiosteal	0.01	0.07	1.5	0.057
						Lung metastasis A	0.23	67.0	1.2	0.26
						Lung metastasis B	0.17	20.0	0.2	0.20
						Femur shaft			3.2	0.034
						Normal kidney			0.4	0.22
						Normal liver			0.5	0.25
						Normal lung			0.3	0.14

us has pointed out previously that there are numerous and highly significant exceptions to this relation.[11] It is evident from the present figures that the phosphatase activ-

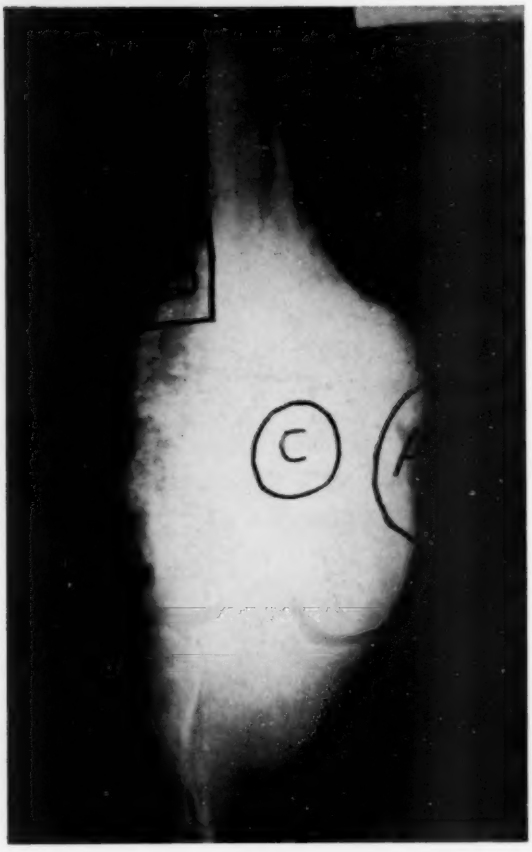

FIG. 1

ity of tumor tissue is an indication of the activity of its mineralization mechanism at the time of examination as is shown by radioactive phosphorus deposition, while the degree of mineralization which is found is an indication of the perhaps quite different activity at some previous time. In this case the dense central tumor probably originally possessed a high phosphatase activity which had enabled it to lay down bone, but this had decreased following roentgen therapy, so that the rate of deposition of phosphorus was low at the time the determinations were made. The more recently formed portions of the tumor, on the other hand, still possessed an active mineralization mechanism.

Histological sections of these specimens were reviewed by Dr. F. W. Stewart who supplied the following report:

Area A. All tumor, but mixed in type—partly sclerosing, calcified, partly cellular, and osteolytic, partly chondrosarcomatous.

Area B. Chondrosarcomatous and calcifying, sclerosing.

Area C. Mainly calcified sclerosing, but there are also remains of previous bone structure with the interstices invaded by osteoid sarcoma tissue.

There is thus no close relation between histological picture and phosphatase activity.

Case III, M. B., a woman, aged fifty-four, had a huge osteogenic sarcoma arising in the middle of the left fibula (Fig. 2), for which she had received no treatment except diathermy and ultraviolet light. Her serum phosphatase was 11.5 units per 100 cc. (lowest postoperative reading 3.1). She received 0.546 mc. radioactive phosphorus by mouth fifty-two hours before amputa-

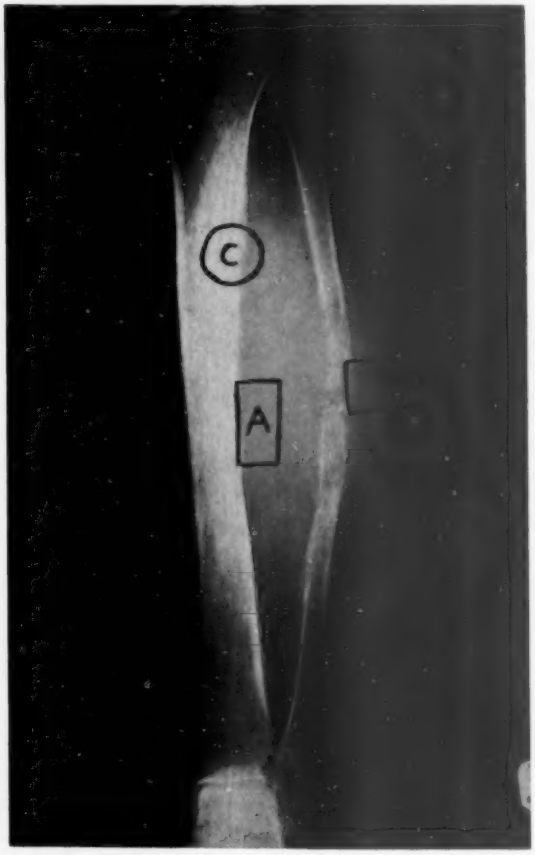

FIG. 2

tion. As in Case I there was a great difference in the phosphatase activities of different portions of the tumor, and the deposition of radioactive phosphorus both in tumor and normal bone was a function of the alkaline phosphatase. If we examine the actual absorption ratios in the 2 cases, however, we note a difference which may be significant. Thus, sample A, Case I and sample B, Case II, had nearly the same phosphatase activities, yet sample A fixed nearly six times as much radioactive phosphorus as sample B in only one-third the time. While absolute reliance cannot be placed on comparisons of absorption ratios in different patients, yet some condition seems to have been present in Case III which prevented mineralization from taking place as rapidly as would be expected from the phosphatase activity. This possibility will be discussed in more detail later.

Case V, H. G., a rapidly growing boy of thirteen, had an osteogenic sarcoma of the lower left femur which had extended up the shaft. He received preoperative roentgen irradiation totalling 3,275 r to the main tumor and 4,100 r to the extension in the shaft. This resulted in a drop in the serum phosphatase from 16.5 units per 100 cc. to 10.3 units, a normal value for his physiological age. He received 0.50 mc. radioactive phosphorus three days after the completion of roentgen therapy and six days before amputation. On histological examination the tumor was found to show no changes attributable to irradiation. The alkaline phosphatase activities of three portions of the tumor was lower than that in most osteogenic sarcomas, but was high enough to show that roentgen inactivation was incomplete. There was an almost direct proportionality between the radioactive phosphorus content and alkaline phosphatase activities of the three specimens of tumor and one specimen of normal bone, and no relation between radioactive phosphorus concentration and acid phosphatase. In this partly inactivated tumor the radioactive phosphorus deposition per unit of tissue phosphatase was much higher than in the previous more active tumors. The difference seems larger than can be accounted for solely by the longer time during which radioactive phosphorus was available, and is further evidence for the presence of a factor inhibiting mineralization.

In Cases II and IV there was a fair correspondence between alkaline phosphatase activity and radioactive phosphorus deposition. Tumor tissue from Case IV was not available. Case VI resembles Case V except that tumor activity was almost completely inhibited by external irradiation.

In all the cases so far discussed and in most of those to be considered later, portions of normal muscle are included for comparison with bone. The average differential absorption ratio for muscle is 0.8 and the range is 0.6 to 0.9 except for Cases IV and VI in which some local peculiarity may have been present. Ratios of about 0.8 were also found for numerous samples of muscle obtained by one of us in the course of another investigation. The ratio is independent of the time after administration of radioactive phosphorus at which the material was taken. Since this ratio is as high as that found in some specimens of normal and tumor bone, and since the glycerophosphatase activity of muscle is almost inappreciable, it is obvious that the relationship which holds in bone between alkaline phosphatase and radioactive phosphorus deposition is not a general one.

The differential absorption ratios for a few specimens of normal marrow are included in the tables to show the general order of magnitude of radioactive phosphorus deposition which may be expected in this tissue. The problem of the relation of radioactive phosphorus therapy to hematopoiesis is considered by one of us in detail elsewhere.[6]

In the next 4 cases the interval between the time when radioactive phosphorus was first administered and that when tissue was obtained was long enough so that changes in the metabolic state of the tumor took place.

Cases VII and VIII (A. C. and J. C.) are so

similar that they may conveniently be considered together. Both were boys in late adolescence with osteogenic sarcomas. The pre-treatment serum phosphatase readings of both were only slightly above those which would be expected in normals of their physiological ages, so the phosphatase activities of the tumors were probably not extremely high at any time. Both patients were given approximately 11 mc. of radioactive phosphorus in divided doses over periods of four weeks during the time when they were receiving roentgen therapy.

The tumor dose in Case VII was 6,450 r from external irradiation. The radiation from radioactive phosphorus received by the two portions of the tumor which were examined amounted to approximately 170 and 400 equivalent roentgens. The irradiation was sufficient to cause extensive destruction of tumor cells as shown on histological examination. Identical small amounts of alkaline phosphatase were found in the two portions of the tumor, but the differential absorption ratios were very different. It is likely that the tumor specimen which had the higher radioactive phosphorus content at amputation had previously had the higher phosphatase activity, and that the phosphatase producing mechanism had subsequently been inactivated by roentgen irradiation.

In Case VIII the tumor dose from external irradiation was 3,700 r and that from radioactive phosphorus a maximum of 400 equivalent roentgens. This was insufficient to cause conspicuous changes in the histopathological appearance of the tumor. It probably caused some drop in tumor phosphatase, since a low reading of 5.5 units per 100 cc. serum phosphatase was found the day before amputation. That the inactivation occurred late was shown by the fact that no significant fall in serum phosphatase had taken place nine days previously. Examination of two specimens of tumor and two of normal bone showed radioactive phosphorus deposition to be a function of the alkaline phosphatase and independent of the acid phosphatase. The storage of radioactive phosphorus per unit of alkaline phosphatase was much higher in normal than in tumor bone, however, despite the probability that, during a part of the time when radioactive phosphorus was available, the tumor phosphatase was higher than that found at amputation. This is in harmony with the suggestion made in the discussion of Cases I, III and V that a factor is present in the metabolism of some osteogenic sarcomas which prevents the full utilization of the bone-forming mechanism. The high isotope ratio in tumor specimen A suggests that the rate of phosphorus turnover was rapid.

Further evidence on the question of the presence of a factor inhibiting mineralization is obtained from examination of the autopsy findings on Case IX (E. C.). The patient, a well developed girl, aged fourteen, presented herself on July 17, 1940, with an osteogenic sarcoma of the lower left femur. The serum phosphatase was 13.2 unit per 100 cc. Readings made after therapy showed that her normal serum phosphatase varied between 5.1 and 7.9 units, so it was evident that the tumor was a phosphatase producer. The parents refused amputation, and from July 20 to August 9, 1940, and again from September 18 to October 16, 1940, the patient was treated with the million volt roentgen-ray machine. The tissue doses to the tumor for the two cycles were respectively 5,580 and 3,520 r, and to the upper femur 2,700 and 2,320 r. There was clinical and roentgenographic evidence of cessation of tumor activity, and at autopsy eight months after the beginning of external irradiation histological examination of the primary tumor showed "only small foci containing questionably viable cells of chondrosarcomatous structure." From November 17, 1940, to January 24, 1941, the patient received prophylactic radioactive phosphorus therapy, the total dose being 19.0 mc. Prophylaxis was unsuccessful, she developed massive lung metastases during the administration of the isotope and died March 29, 1941, sixty-six days after the last dose. The serum

phosphatase did not rise with the growth of the metastases.

At autopsy two portions of the primary tumor and two metastatic areas from the lungs were obtained. The inactive primary exhibited the same type of irregularity which was observed in Case VII, and the differential absorption ratios were not high. Both portions of metastatic tumor had high alkaline phosphatase activities, yet the tissues were not mineralized and contained less radioactive phosphorus than the uninvolved femur shaft, even though the activity of the latter was probably somewhat reduced by the irradiation it had received. The differential isotope ratios in the metastases were of the same order of magnitude as those of the kidney, liver, and normal lung of this patient, or of those found for normal muscle in numerous other cases. The findings in this case are an extreme example of the similar differences found in Cases I, III, V and VIII.

The observations on this patient tend to discourage the use of radioactive phosphorus in the treatment of osteogenic sarcoma. As explained in the introduction, we anticipated that the radiation dose which could be administered to the primary lesion by means of radioactive phosphorus alone would not be sufficient to destroy so radioresistant a tumor. We hoped, however, that if the microscopic metastases fixed radioactive phosphorus in as great a concentration as the primary, the damage due to irradiation added to that of unfavorable environment might be sufficient to prevent their becoming established. In this patient metastases grew to demonstrable size during a full course of radioactive phosphorus therapy, and the postmortem findings showed that they were not mineralized and had not stored radioactive phosphorus in concentrations large enough to be of therapeutic significance. It is, of course, possible that the low differential absorption ratios found at postmortem were the result of early storage of phosphorus followed by loss, rather than of primary failure of absorption. If this were true, the presence of the isotope during the period when its radioactivity had not been greatly diminished by decay would have resulted in the administration to the tissue of much larger radiation doses than would be indicated by the late observations. Even if this were so, the irradiation was insufficient to prevent the growth of the metastases. The inability of the metastatic tissue to fix radioactive phosphorus permanently indicates a profound difference between its metabolism and that, for instance, of the uninvolved femur of the same patient. Final evaluation of the results of radioactive phosphorus therapy in osteogenic sarcoma must await further clinical observations, but the experimental findings at present indicate that there are serious limitations to the usefulness of the method.

Table II summarizes the results of the examination of tissues other than osteogenic sarcoma.*

Case X, F. M., a boy, aged eight, had numerous calcified bands in the neck, shoulders and back. As he also showed congenital abnormalities of the hands and feet the disease was diagnosed as myositis ossificans progressiva. His serum phosphatase was 12.7 units per 100 cc., or somewhat higher than was to be expected from his apparent rate of body growth. He was given 0.434 mc. of radioactive phosphorus, and eight days later a portion of the mineralized area in the back was excised together with adjacent normal muscle. The two tissues were sharply demarcated without any intergradation. The microscopic report on the mineralized specimen was "Dead bone in material which looks like tendon or aponeurosis." The specimen contained bone type phosphatase in higher concentration than we have ever observed in normal bone, and its differential absorption ratio was very high. The unaffected muscle was normal both in phosphatase activity and absorption ratio. The disorder, while pro-

* We are indebted to Dr. G. T. Pack of the Mixed Tumor Service, Dr. G. H. Twombly of the Endocrine Service, and Dr. Archie Dean of the Urological Service for permission to observe Cases X to XIV inclusive.

TABLE II

DISEASES OTHER THAN OSTEOGENIC SARCOMA

Case No.	Diagnosis	Age and Sex	Serum Phosphatase Units per 100 cc.	Dose P^{32} mc.	Time after P^{32}	Tissue	Tissue Phosphatase		Differential Absorption Ratio	Differential Isotope Ratio
							Acid	Alkaline		
							Units per gram			
X	Myositis ossificans progressiva	M 8	12.7	0.43	8 days	Calcified area	0.09	8.7	9.8	0.20
						Normal muscle	0.03	0.03	0.6	
						Membrane around calcified area			0.1	
XI	Embryonal carcinoma of the testis	M 28		0.50	8 days	Tumor metastatic to lung	1.2	19.0	1.4	0.89
						Tumor metastatic to liver	1.4	27.5	2.0	1.0
						Normal liver	0.40	0.75	2.6	
						Normal muscle			0.7	
XII	Fibromyomatous prostate	M 54	Acid 0.24 Alkaline 3.6	0.25	11 days	Prostate	570.0	0.01	1.0	
						Bladder muscle			0.9	
XIII	Spindle cell sarcoma buttock	F 45		0.50	12 days	Ossified tumor	0.05	1.0	1.8	
						Necrotic soft tumor	0.15	0.9	0.3	
XIV	Cancer breast metastatic to bone	F 60	13.6	0.58	36 days	Tumor metastatic to liver	0.23	0.06	0.4	
						Vertebra infiltrated with tumor	0.16	1.20	6.0	
						Normal femur shaft	0.02	0.03	0.3	
						Normal muscle			0.6	
XV	Endothelioma of bone	F 14	3.6	1.42	98 days	Primary tumor	0.75	0.20	0.6	0.06
						Tumor metastatic to rib	0.75	2.3	5.6	0.15
						Normal rib	0.25	0.45	1.0	0.009
						Tumor metastatic to soft parts	1.5	0.15	0.3	0.11
						Slightly involved vertebra	0.50	0.55	0.7	0.025
						Normal kidney			0.5	0.064
						Normal spleen			0.8	0.20
						Normal liver			0.4	0.17
						Normal muscle			0.9	0.40

gressive, was thus not generalized in the sense that the bone type of phosphorus metabolism apparently was not present in the muscles prior to the onset of mineralization.

Case XIII, R. B., resembles Case X in that a bone type of phosphatase was found in abnormal tissue arising in muscle. In this case two portions of a spindle cell sarcoma which was probably of muscle type contained only small amounts of acid phosphatase and about 1 unit per gram of alkaline phosphatase. The mineralized portion, which was pronounced on histological examination to be ossified tumor, not true bone, had a differential absorption ratio of 1.8. The necrotic portion, although it had retained its phosphatase activity, was not mineralizing at the time of observation, and had a differential absorption ratio of only 0.35. The contrast between the two portions of this tumor is analogous to that found in different types of osteogenic sarcoma. Why the tissues of these two patients developed a bone type of metabolism and a tendency to mineralization must remain a subject for further study.

In Case XI (P. S.) a bone type of phosphatase was found in a tumor not of bone origin which showed no tendency to mineralize. The patient, a man, aged twenty-eight, had an embryonal carcinoma of the testis with generalized metastases. His serum phosphatase was unfortunately not determined. He was given 0.50 mc. of radioactive phosphorus eight days before death. At autopsy it was found that two metastatic areas in the soft parts contained moderate amounts of acid phosphatase and large amounts of alkaline phosphatase. Despite this they fixed less radioactive phos-

phorus than the uninvolved liver and only two to three times as much as normal muscle. The discovery of the high alkaline phosphatase activity of this tumor tissue was entirely unexpected, and, as far as we are aware, has not been previously reported. The function of this alkaline phosphatase is unknown, but it obviously does not result in the storage of phosphorus.

Case XII (M. L.) illustrates the fact that the well known high acid phosphatase of the prostate is similarly not concerned with the storage of phosphorus.

Case XIV (S. S.) was a woman, aged sixty, with widespread bone metastases from carcinoma of the breast. That the metastases were of the type which elicits considerable bone reaction was shown not only by the roentgenographic appearance, but by the fact that her serum phosphatase was markedly elevated. She received 0.58 mc. of radioactive phosphorus thirty-six days before death. At autopsy the usual small amount of acid phosphatase and very small amounts of alkaline phosphatase were found in metastasis to the liver. Radioactive phosphorus storage was low. In the portion of vertebra infiltrated with carcinoma, which was composed of about equal parts of tumor and bone, there was a moderate amount of alkaline phosphatase and a high concentration of radioactive phosphorus. It is evident from this observation that while a high deposition of radioactive phosphorus may be expected in areas of bone invaded by metastatic disease, the isotope is not taken up mainly by the tumor in the bone, but rather by the reacting bone surrounding the tumor. Since radioactive phosphorus deposited in the bone will deliver irradiation to adjacent tumor tissue, it is possible that this agent may be of value in the treatment of metastases to bone from radiosensitive tumors, provided the metastases are of a type which stimulates the production of phosphatase by the bone.

Case XV (M. T.) a girl, aged fourteen, with endothelioma of bone, is included in Table II rather than in Table I because the tumor arises from the endothelial elements included in the bone rather than from the bone itself, and because its phosphatase is not of bone type but resembles that found in many sorts of carcinoma and in normal kidney and liver. The patient received 1.42 mc. of radioactive phosphorus ninety-eight days before death. At autopsy the primary tumor, which had received heavy roentgen irradiation, was found not to contain bone phosphatase, and histological examination showed that the bone in this area had been devitalized. The radioactive phosphorus content was low. A metastatic area in the rib, where active bone proliferation was taking place, resembled the vertebral metastasis in Case XIV in having comparatively high concentrations of alkaline phosphatase and of radioactive phosphorus. The acid phosphatase in this specimen was due mainly to the tumor infiltrating the hyperplastic bone, although extracts of normal rib, like those of normal vertebrae, always have significant acid phosphatase activities owing to the impossibility of effecting a complete separation of marrow from bone. This is seen in the specimen of rib in this patient. The tumor metastatic to soft parts, which contained mainly acid phosphatase, had fixed less radioactive phosphorus than the normal soft tissues examined. In the type of phosphatase which it contains and in the way in which it stores radioactive phosphorus, endothelioma of bone thus resembles many normal and pathological soft tissues rather than normal bone or osteogenic sarcoma.

DISCUSSION

The results of this investigation show that radioactive phosphorus is deposited in normal and hyperplastic bone and in many areas of osteogenic sarcoma at a rate which is a function of the alkaline phosphatase activity of the tissue. In some high phosphatase osteogenic sarcomas, however, unknown factors are present which prevent the deposition of calcium phosphate. This greatly limits the probable usefulness of

radioactive phosphorus as a therapeutic agent for tumors of this type.

The discovery that conditions exist in osteogenic sarcoma tissue which prevent mineralization despite the presence of a powerful mechanism for promoting mineralization is an important one. This is especially true since we have the clinical impression that a patient with a poorly calcified tumor and a very high serum phosphatase has an exceedingly bad prognosis. It is hoped that future work may demonstrate the nature of the factor which prevents the satisfactory utilization of bone phosphatase, and which is associated with a high degree of malignancy.

While the large body of indirect evidence obtained by many investigators has left little doubt that the function of the alkaline phosphatase of bone is to promote the deposition of calcium phosphate, the direct evidence obtained in the present work constitutes a proof of the hypothesis. We have failed to demonstrate any relation between the acid glycerophosphatase of any tissue and the deposition of radioactive phosphorus. The function of the acid glycerophosphatases thus remains a subject for further investigation. This is also true of the alkaline glycerophosphatases of tissues other than bone, particularly that of embryonal carcinoma of the testis.

SUMMARY

In normal bone and in many specimens of osteogenic sarcoma tissue the deposition of radioactive phosphorus is a function of the alkaline glycerophosphatase activity.

In some osteogenic sarcoma tissue an unknown condition exists which prevents the storage of radioactive phosphorus despite an intense alkaline phosphatase activity. This condition seems to be associated with a high degree of malignancy.

No quantitative relation was found between the acid glycerophosphatase activity of any tissue and its capacity to store radioactive phosphorus.

Muscle extracts have minimal alkaline phosphatase activities and muscle tissue stores moderate amounts of radioactive phosphorus. A specimen of spindle cell sarcoma of muscle type and a specimen of myositis ossificans tissue were found to contain phosphatase of bone type and to store abundant radioactive phosphorus.

Favorable results from the use of radioactive phosphorus in the treatment of patients with bone tumors can be hoped for only when there is an elevation of serum phosphatase or other evidence that new bone can be formed. Even in apparently favorable cases therapy may be unsuccessful owing to the presence of factors preventing mineralization.

The authors wish to express their thanks to Miss Mildred Moore and Miss Audrey Anscheutz for technical assistance in this investigation; to Dr. F. W. Stewart for reviewing the histological sections, and to Mr. L. D. Marinelli for aid in making the physical measurements. Acknowledgment is made to the Works Projects Administration of New York City for assistance rendered under Official Project No. 24

REFERENCES

1. BODANSKY, A. Phosphatase studies. II. Determination of serum phosphatase. Factors influencing accuracy of the determination. *J. Biol. Chem.*, 1933, *101*, 93–104.
2. COLEY, B. L., and POOL, J. L. Factors influencing prognosis in osteogenic sarcoma. *Ann. Surg.* 1940, *112*, 1114–1128.
3. FRANSEEN, C. C., and MCLEAN, R. Phosphatase activity of tissues and plasma in tumors of bone. *Am. J. Cancer*, 1935, *24*, 299–317.
4. HAVEN, F. L., and BALE, W. F. Fate of phospholipid injected intravenously into the rat. *J. Biol. Chem.*, 1939, *129*, 23–32.
5. HEVESY, G. C. Application of radioactive indicators in biology. *Ann. Rev. Biochem.*, 1940, *9*, 641–662.
6. KENNEY, J. M. Radioactive phosphorus as a therapeutic agent in malignant neoplastic disease. *J. Am. M. Ass.*, to be published.
7. MARINELLI, L. D. Dosage determinations with radioactive isotopes. AM. J. ROENTGENOL. & RAD. THERAPY, Feb., 1942, *47*, 210–216.
8. MOORE, M. L. Unpublished work.
9. PREGL, F., and ROTH, H. Quantitative Organic Microanalysis. P. Blakiston's Son & Co., Philadelphia, 1937, pp. 126–130.
10. SCOTT, W. W. Standard Methods of Chemical Analysis. D. van Nostrand Co., New York, 1925, p. 372.
11. WOODARD, H. Q., and HIGINBOTHAM, N. L. Serum and tissue phosphatase determinations as

an aid in evaluating radiation therapy of bone tumors. *J. Am. M. Ass.*, 1941, *116*, 1621–1627.
12. Woodard, H. Q., Twombly, G. H., and Coley, B. L. Study of serum phosphatase in bone disease. *J. Clin. Investigation*, 1936, *15*, 193–201.

Discussion on Papers of Drs. Oughterson, Plaut and Lawrence; Marinelli; Kenney, Marinelli and Craver; and Woodard and Kenney

Dr. U. V. Portmann, Cleveland, Ohio. Host-tumor relationships are extremely complex. We can recognize some of them by morphologic changes in the tissues surrounding tumors or what Dr. Oughterson chooses to call their "environment." Although these changes may be defensive measures on the part of the host, we know little or nothing concerning the mechanism which brings them about. We have learned that cells in vitro or in vivo which are in active stages of cellular division are more susceptible to radiation than those that have become physiologically and morphologically differentiated. This would seem to indicate a direct destructive action of radiation.

However, we observe clinically that tumors in anemic and cachectic patients do not respond well to irradiation. I know of no satisfactory explanation of this, but it probably represents host-tumor relationships having to do with indirect effects of radiation on the part of the tumor environment.

No doubt, tumors do excite reactions in the host. For example, fibrous tissue about them is produced physiologically. However, irradiation also may cause increased production of fibrous tissue, as a result of which tumor growth is restricted. When this reaction to irradiation is established, neoplastic cells in the fibrous tissue never seem to be radioresistant. It is questionable whether this resistance becomes an inherent property of the neoplastic cells, or an inability of the host to react to their presence or the radiation.

Another important factor in regard to host-tumor relationships influencing the effects of irradiation is the matter of origin of tumors. For example, neurogenic tumors are almost as radioresistant as nerve tissues, and those originating in gonads are as radiosensitive or more so than the reproductive organs.

It seems to me that the experiments of Dr. Oughterson and his colleagues give us additional information about the host-tumor relationships and tumor environment as influencing the reaction to irradiation. Their method of approach is interesting. However, I am not convinced about one of their conclusions, although their other ones are justified. They believe that they have found that irradiation augments the natural resistance factors to tumor growth. I am not sure that this has been proved if systemic resistances or reactions and not only local reactions are taken into consideration. Also, it seems to me that their experiments suggest the possibility of hereditary factors influencing host-tumor relationships.

Dr. Shields Warren, Boston. I particularly enjoyed Dr. Oughterson's paper because of my very deep interest in the relationship between the host and the tumor. The ingenious series of experiments that he reports here gives us some very helpful added information. It was particularly helpful that he has stressed the difference in the behavior of tumor cells in vitro and in vivo. Certainly it is very fortunate for all interested in therapy that cells growing in the body can be damanged or killed with doses appreciably less than those required to do a comparable amount of damage in vitro.

There were several points that I think would be helpful if Dr. Oughterson could clarify for us. First, what is the rate of growth of the tumor in the initial strain and in the hybrid? Was it the same? And was there any appreciable difference in the microscopic picture as evidenced by stromal reaction and leukocytic infiltration?

I am inclined to agree with Dr. Portmann in questioning the augmentation of the natural factors of immunity because it has been shown that one way in which tumors can be made to grow in foreign species is by subjecting that foreign species to roentgen irradiation. That is, if one irradiates a rat, one can transplant a mouse tumor successfully when it cannot be done to the non-irradiated animal. That would indicate a lessening of natural resistance rather than an increase of it.

With regard to the papers dealing with radioactive phosphorus, I can only say that I learned a great deal and was deeply interested in the detailed studies that have been carried out. I have attempted in 2 cases of Hodgkin's disease to follow this means of therapy. The longer case has now gone nearly a year and I think that the results are comparable at least with those that could be obtained from roentgen irradiation.

In Dr. Woodard's tables I was particularly interested in the high content of the phosphorus in muscle and wonder whether this might not be associated with the carbohydrate metabolism and the formation of hexose phosphate there as well as with the phosphatase content of the muscle tissue.

DR. FREDERICK W. O'BRIEN, Boston. I suppose I was asked to discuss Dr. Kenney's paper and that of his associates because of my interest in the lymphoma group. I would like to congratulate them on their very conservative presentation. It is so lacking in the fanfare that we have almost become accustomed to of late when new things are talked about.

I had a preliminary paper from Dr. Kenney which I read over and perhaps I misread it but my recollection was that at that time they were not treating successfully large groups of nodes and I was a little surprised when I saw the conclusions on the lantern slide. Perhaps in his discussion he will tell us something about the size of the nodes successfully treated later.

As I see it, the present status of the treatment of lymphosarcoma with radioactive phosphorus is not unlike the treatment of the lymphoma group by teleroentgen therapy, that is, when we have enlarged glands or nodes the remedy is not applicable.

DR. NORMAN L. HIGINBOTHAM, New York. I believe Dr. Woodard's presentation is full of considerable significance, particularly in the treatment of osteogenic sarcoma and other malignant bone tumors. When P^{32} first came to our attention we were greatly impressed with its possibilities in the treatment of bone tumors because we felt that of all tissues perhaps bone would absorb this element more readily than other tissues would. With that in mind, we felt inclined to try it with considerable hope of improving our results.

Dr. Woodard has shown that the P^{32} absorption is greatest in bone where the phosphatase content is highest. As certain osteoplastic osteogenic sarcomas have a high phosphatase activity we would expect marked effect in such instances and study of a larger series is necessary to fully evaluate this observation.

Adequate external irradiation will effect a marked decrease in the phosphatase activity of a bone tumor. If, therefore, we seek maximum absorption of P^{32} it would seem logical to administer the P^{32} before any external irradiation is given, or to give it in those cases in which amputation is to be performed without preoperative irradiation. To date P^{32} has usually been given in conjunction with preoperative irradiation so that I do not believe we have attained its maximum effect. In further therapeutic tests it might be more satisfactory to administer P^{32} as the initial therapy—previous to amputation or preoperative irradiation. A good deal more investigation along these lines must be done and I believe the work thoroughly justifiable.

The possible effect of P^{32} in preventing or destroying metastases also merits thorough investigation. It is reasonable to assume that tumor cells break away from the primary tumor, get into the general circulation, are deposited in the tissues, and grow wherever conditions are favorable for their deposition and growth. In osteogenic sarcoma the lungs seem to show a specific predilection for metastatic activity. It is possible that P^{32} can be given in large enough safe doses to destroy these metastasizing cells or prevent their lodgment and growth in the lungs. This phase of the study also merits much more research.

DR. EDITH H. QUIMBY, New York. There is one question that has been raised by a number of people in talking with me about this subject of dosage in radioactive substances. That is, how can we express tissue doses in terms of tissue roentgens or equivalent roentgens or anything of the kind when the amount of radiation varies so sharply from place to place within the tissues?

Actually this fact does not make any difference as far as expression of dosage is concerned. One roentgen means the formation of a certain number of ion pairs *per unit mass* of air under certain specified conditions; there is nothing implied about what happens a short distance away.

I think the trouble is that the radiologist unconsciously pictures a gradual change in radiation intensity such as that in a beam of roentgen rays passing through the body.

If, however, we start our picture with interstitial irradiation with seeds, we easily see how we can have a spotty distribution of dosage; yet we know that we can express in gamma roentgens the dose delivered by seeds at any particular point. If seeds, for instance, are implanted in a node, the dose within the node is greater than that outside it.

Now reduce this picture to microscopic di-

mensions. The sources of radiation are the phosphorus atoms which have been taken up by the cells—some kinds of cells have more than others, those will receive larger doses.

The actual expression of these doses in terms of "equivalent roentgens," as presented by Mr. Marinelli, is a preliminary effort to bring them into line with roentgen- and gamma-ray doses, for purposes of comparison. On a basis of tracer studies combined with such dosage calculations it is possible to form an opinion as to whether a given radio-isotope should be expected to deliver a desirable quantity of radiation into certain cells or organs, while that in others is maintained below the danger point.

Dr. Oughterson (closing). I want to thank Dr. Portmann and Dr. Warren for their very kind remarks. I am only too well aware that such a nebulous subject gives opportunity for criticism of the methods employed in this investigation. We have primarily tried to direct attention to the host as an important factor in determining the response to irradiation in addition to the other factors which have been mentioned. By this means we hope gradually to get at the factors which may be influencing the cell. We have used the term "host" in the broad sense since we do not as yet know enough of the chemistry of the cell as influenced by irradiation. However, it is self-evident that the factors in the host which modify the response to irradiation must ultimately be explained in chemical terms.

One of the objections which may be raised to these experiments is that we are primarily dealing with a problem in genetics. However, previous investigators have indicated that normal tissue transplants react in the F_1 generation as in the parent strain. If this is correct, then the differences found in the F_1 generation may not be explained on a genetic basis but rather on the specific tumor-host relationship.

We freely admit that one cannot draw too many conclusions from this until we can get the problem out of the genetic field entirely. For this reason we attempted to modify the response by non-genetic means.

As regards the morphological changes in the stroma, we have pointed out in previous publications that these are present and parallel the difference in response to roentgen irradiation. There is also a significant but not marked correlation with the rate of growth of the tumor.

The use of such very general terms as "augmentation of resistance" is vague and undesirable but likewise is such a term as the "degeneration theory" used to explain the effect of roentgen irradiation. We can only hope that eventually we may arrive at expressions which are a little more specific in the light of experimental fact.

Dr. Woodard (closing). In answer to Dr. Warren's question, I presented the factors which govern the deposition of P^{32} in tissues in barest outline, pointing out how only P^{32} was used to build new tissue or to replace worn out tissue.

Many tissues, however, contain substances which are elaborated there for special purposes. Special functions are either fulfilled in the tissue or the substances are carried elsewhere. For instance, the uptake of P^{32} in the liver is extremely rapid after a single dose, owing to the formation of phospholipids which are stored temporarily in the liver and then carried to other parts of the body.

Similarly in muscle, Dr. Warren is undoubtedly right in supposing that a large portion of the P^{32} in the muscle is present as hexose phosphate. This view is upheld by the observation that P^{32} content of the muscle relative to the body as a whole remains essentially constant for periods of a month or so after administration of a dose. In this case the amount which is actually fixed in the muscle to replace lost muscle substance is extremely small compared to that which is turned over rapidly in the muscle buf present at all times as hexose phosphate or some related compound. One of the things I hope to do is to study the hexose phosphatase content of some of these tissues rather than simply the beta glycerophosphatase content which I have been hitherto investigating.

I want to thank Dr. Higinbotham for his discussion. Lest I should seem to be at variance with him in discouraging all idea of the use of P^{32} in therapy, I should point out that in the treatment of endothelioma of bone we have had two other cases where the pick-up was rather better than it was in the autopsy case which I showed you, and that we can expect that endothelioma tissue which is growing rapidly will take up P^{32} rapidly simply by virtue of its growth rate. As endothelioma of bone is radiosensitive, this may do some good.

Also, in the autopsy case on osteogenic sarcoma which I showed you, there was no evidence of a differential uptake in the metastases.

The patient died of those metastases despite fairly adequate therapy. That does not prove that in some other cases the uptake in the metastases may not be large enough to do some good. We hope it will, and one of the operative cases that I showed you who had an excessively bad prognosis and a serum phosphatase which failed to fall to normal immediately after amputation, has now gone seven months without evidence of disease after P^{32} therapy. That is not long but her serum phosphatase is normal and it is possible that the P^{32} has done some good.

We are dealing, in all these patients, with a disease which has a very bad prognosis anyway and we are planning to go on with the therapy in the hope of bettering the condition of some of them. While we may report some failures now, we cannot report our successes, if any, until two or three years have passed, and I hope by that time we may have some to report.

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ROENTGENOLOGIC MANIFESTATIONS OF TUMORS OF THE SMALL INTESTINE*

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THE last decade has witnessed a renewed interest in the application of roentgenologic methods to the diagnosis of lesions of the small intestine. It is of course true that, before this, many roentgenologic examinations of the small intestine were conducted, and that in the aggregate many lesions were discovered even in the early years of gastrointestinal roentgenology, for the manner of conducting this examination has been changed little in principle since Rieder's time, and the pioneers came early to a clear understanding of how roentgenologic data were to be translated into terms of pathologic anatomy.

But the early interest seems not to have been kept lively. After all, the incidence of lesions of all types, blastomatous and nonblastomatous, is very low in the small intestine, and the roentgenologic examination of the small intestine, compared to that of the divisions of the alimentary tract above and below it, is an arduous and time-consuming procedure. So, presumably, it came about that some roentgenologic examiners became content to perform a more or less perfunctory type of examination. Others became unwilling to perform the examination at all, reasoning that if the clinical syndrome indicated an intestinal lesion severe enough to bring the patient to the physician, the diagnosis might as well be made by exclusion, that is by eliminating the stomach, duodenum and colon as possible sites of the offending lesion. They felt, quite justifiably, that the efficiency of their method in the diagnosis of organic disorders of these upper and lower divisions of the alimentary tract was rapidly becoming better and better established, whereas it seemed possible to learn comparatively little about the roentgenologic manifestations of the lesions affecting the lower part of the duodenum, the jejunum and the ileum.

And it must be admitted that this reasoning has merit. There are certain clinical syndromes in the presence of which the diagnosis of "gastrointestinal lesion" is imperative, even when all preoperative objective diagnostic tests have failed to exhibit the pathologic process responsible for them. Proved gastrointestinal bleeding is an outstanding example of such an imperative clinical situation. After the esophagus, stomach, duodenum and colon have been eliminated as possible sites of the hemorrhagic lesion by the judicious use of roentgenologic and endoscopic tests, it is certainly justifiable to conclude that if a gastrointestinal lesion exists at all, the small intestine is harboring it. Under most circumstances sufficient grounds for the institution of diagnostic laparotomy might thus be established.

It is better, of course, first to exhaust all other means of localizing the lesion, and we propose to show that a special roentgenologic examination of the small intestine can be made to yield very satisfactory diagnostic results frequently enough, at least, to warrant its application whenever the condition of the patient permits it. With this in mind we selected for study the cases of benign and malignant tumor of the small intestine encountered at the Mayo Clinic up to and including the year 1939. C. W. Mayo recently published an analysis of 108 cases of malignant lesion of the small intestine. He made the material on which his study was based available to us, and in addition to the cases therein represented we selected for study the 41 cases of benign tumor of

* Read at the Forty-first Annual Meeting, American Roentgen Ray Society, Boston, Mass., Oct. 1–4, 1940.

TABLE I

MALIGNANT LESIONS OF THE SMALL INTESTINE, 1907 TO 1939, INCLUSIVE (FROM MAYO[1])

Site and Pathologic Lesions

Lesion	Site						
	Duodenum	Jejunum	Ileum	Meckel's Diverticulum	Multiple	Not Specified	Total
Adenocarcinoma	23	31	21		4	1	80
Leiomyosarcoma	2	2	1	4		1	10
Other lesions		1*	1†				2
No pathologic specimen	4	6	4			2	16
Total	29	40	27	4	4	4	108

* Epithelioma, multiple, melanotic type.
† Hemangio-endothelioma.

the small intestine encountered at the Mayo Clinic in the same interval, the years 1907 to 1939, inclusive.

Mayo found (Table I) the jejunum to be the segment of the small intestine most frequently affected by malignant tumors, while the other segments, the duodenum and ileum, were involved one about as frequently as the other. The duodenum, however, seems to be a favored site for benign lesions, such lesions occurring less frequently in the jejunum and ileum (Table II). The premise for this conclusion may not be entirely valid, however, since many of the benign tumors (39 per cent) were discovered incidentally in the course of operations for duodenal ulcer, under which circumstances this division of the small intestine is comparatively well exposed for exploration.

Adenocarcinoma was by far the most frequently encountered histopathologic type of malignant tumor of the small intestine in Mayo's series, while most of the rest of the cases were leiomyosarcoma (Table I). A greater variety of histopathologic types of benign tumor is seen (Table II) but no one type plays so dominant a rôle as adenocarcinoma does among the malignant tumors. The high incidence of tumors of the

TABLE II

BENIGN LESIONS OF THE SMALL INTESTINE, 1907 TO 1939, INCLUSIVE

Site and Pathologic Lesions

Lesion	Site					
	Duodenum	Jejunum	Ileum	Multiple	Not Specified	Total
Adenoma	6	2	3			11
Myoma	8	4	2			14
Lipoma		2	2			4
Fibroma	1	1	2			4
Hemangioma	2		1			3
Osteochondroma					1	1
No specimen		1	1	1	1	4
Total	17	10	11	1	2	41

smooth muscle, both benign and malignant, is noteworthy. The distribution of the various histopathologic types of malignant and benign lesions in the several divisions of the small intestine is also shown in Tables I and II.

In his analysis Mayo discussed very briefly the accuracy of the preoperative diagnosis in cases of malignant tumor of the small intestine, and while he noted that the preoperative or prenecroscopic diagnosis was made in but 26 of the cases (24 per cent), he stated that the accuracy had greatly improved in recent years. An accuracy as low as this is neither very flattering nor very encouraging for a roentgenologic examiner to contemplate. Some extenuating circumstances were brought out, however, in the analysis of those cases in which the small intestine was actually examined roentgenologically. It was discovered, for instance, that in 26 of the cases analyzed by Mayo no roentgenologic examination was made of any part of the gastrointestinal tract, and in 46 no special examination of the small intestine was requested, although the stomach or colon or both were examined roentgenologically.

There are many reasons, good and sufficient for the most part, for this apparent failure to use the full complement of roentgenologic examination of the gastrointestinal tract. In 4 instances, for example, important, and later substantiated, lesions were discovered in the colon and stomach, and the roentgenologic search ended there; in other instances the patients were first seen in the state of actual or impending intestinal obstruction, or were otherwise too ill to be submitted to roentgenologic examination. Other patients were seen in the early years before any kind of satisfactory roentgenologic examination of the gastrointestinal tract, and particularly of the small intestine, was developed. Thus in two-thirds of the cases in Mayo's series it may be said that the failure to arrive at a satisfactory preoperative diagnosis cannot be justifiably ascribed to failure or inadequacy of the roentgenologic method.

There were 36 cases in which the diagnosis should have been made roentgenologically. In 4 of these the lesion was overlooked completely. In the remaining 32 cases, 89 per cent, the presence and site, at least, of a pathologic process were determined roentgenologically. Among these were 8 more or less serious misinterpretations, all of them in cases of carcinoma of the first portion of the duodenum. The roentgenologic diagnosis was duodenal ulcer with or without obstruction in 4, "obstructing lesion at the outlet of the stomach" in 3, and "carcinoma of the stomach" in one. In the remaining 24 cases of malignant tumor of the small intestine the roentgenologic diagnosis was "obstructing lesion" in 9, "ulcerating lesion" in 4, "carcinoma" in 6, and "lesion" described and located in five. We consider these to be satisfactory roentgenologic diagnoses for practical clinical purposes. If the misinterpretations made in the cases of carcinoma of the first portion of the duodenum are to be considered diagnostic errors, the percentage of accuracy of the roentgenologic method falls from 89 per cent to 67 per cent.

To get an estimate of the diagnostic efficiency of the roentgenologic method in cases of tumor of the small intestine in more recent times, we selected for special analysis those cases encountered at the Mayo Clinic in the last decade, the years 1930 to 1939 inclusive. There were 62 cases, 50 of which were of malignant tumor, and 12 of benign tumor. Of these, 26 were not pertinent from the viewpoint of roentgenologic diagnosis: in 5 of them no roentgenologic examination of any part of the gastrointestinal tract was made; in 17 no roentgenologic examination of the small intestine was made, although roentgenologic examination of the stomach or colon or of both was made; in 4 a clinically important lesion was diagnosed correctly in the stomach, colon or duodenum.

There remain then 36 cases (62 minus 26) for analysis from the viewpoint of diagnostic accuracy. In 5 of these, 14 per cent, the lesion of the small intestine was over-

looked at the roentgenologic examination. Three of these lesions proved on pathologic examination to be adenocarcinoma; one, lipoma; one, submucous hemangioma, 6 mm. in diameter, discovered at pathologic examination of a resected specimen of ileocecal granuloma with persistent postoperative fecal fistula. We are inclined to consider the roentgenologic diagnosis in the remaining 31 cases as satisfactory. This does not mean that a precise pathologic diagnosis was made in each instance, but it does mean that the lesion was at least recognized and located where the tumor was later found at operation. Roentgenologic diagnoses such as "obstructing lesion," "ulcerating lesion," "polypoid lesion" and "malignant lesion" are included. Included also were 4 cases in which the roentgenologic diagnosis was "duodenal ulcer," and 2 in which the roentgenologic diagnosis was "obstructing lesion at the outlet of the stomach," in all of which later surgical exploration revealed a tumor in the first portion of the duodenum. Thus in the decade just passed our roentgenologic examination disclosed the presence of a lesion and located its site in 31 of 36, or in 86 per cent of the cases. In one of the 5 cases in which the intestinal tumor was overlooked, the tumor was purely an incidental finding at pathologic examination of a specimen removed surgically for an entirely extraneous reason.

RELATION OF SITE OF LESION TO ACCURACY OF ROENTGENOLOGIC DIAGNOSIS

We also analyzed the 62 cases of tumors of the small intestine observed in the last decade to determine the relation of the site of the lesion to the accuracy of the roentgenologic diagnosis.

Duodenum. There were 21 cases in which the tumor was located in the duodenum. In 15 of these the tumor was malignant; in 6 it was benign. Four of the 21 cases were not considered relevant: 3 were cases of duodenal or gastrojejunal ulcer correctly diagnosed roentgenologically, the tumor having been discovered incidentally by the pathologist examining the surgical specimen; in the other case no roentgenologic examination of the small intestine was performed. There are thus 17 cases (21 minus 4) for study from this viewpoint.

In 7 cases the tumor was in the first portion of the duodenum. In one the roentgenologic diagnosis of tumor was correctly made; in one, the diagnosis was "duodenal ulcer with crater"; in 2, "obstructing lesion at the outlet of the stomach"; in 3, "duodenal ulcer with obstruction." In no instance was the lesion overlooked, but in only one instance was the lesion diagnosed correctly. To one inexperienced in roentgenologic gastrointestinal diagnosis these might seem to be serious misinterpretations; yet when it is known that in this same decade there were roughly 17,000 cases of duodenal ulcer correctly diagnosed in the Section on Roentgenology at the Mayo Clinic, the comparative incidence of tumor in the same segment of the duodenum is practically negligible, and the roentgenologic evidences for tumor would have to be clear indeed before the diagnosis of tumor could be hazarded. It should be noted, too, that 5 of the 7 "misinterpretations" were obstructing lesions in which it is notoriously difficult to determine the exact cause of the obstruction.

In 3 cases the tumor was in the second portion of the duodenum. In one the lesion was entirely overlooked, and in 2 the correct diagnosis was made. While the incidence of primary tumors of the duodenum seems to be lowest in this segment, the incidence of lesions simulating true tumors seems to be relatively high here. It has been our experience that tumors of the head of the pancreas seem most prone to invade this segment and cause ulceration in it, and it is not always easy to determine the true nature of such a lesion.

In 7 cases the tumor was in the third portion of the duodenum, and the lesion was discovered at roentgenologic examination in each instance. In fact, the lesion was identified as tumor in 6 of the cases, and in the other the roentgenologic diagnosis was "obstructing lesion."

Thus, if the misinterpretations noted in the preceding paragraphs are considered to be satisfactory diagnoses, the diagnostic accuracy of the roentgenologic examination for the duodenum can be said to be 94 per cent. Otherwise, the correct diagnosis was made in but 9 of the 17 cases, or 53 per cent.

Jejunum. There were 20 cases in which the tumor was in this segment of the small intestine. Two tumors were benign, and 18 malignant. In one case no roentgenologic examination of any part of the gastrointestinal tract was made; in 6, roentgenologic examination of only the stomach or colon or both was made. There are thus 13 cases for analysis from the viewpoint of roentgenologic diagnosis. In 2 of these, 15 per cent, the lesion was overlooked at roentgenologic examination. In 11, a satisfactory roentgenologic diagnosis was offered. Again such diagnoses as "obstructing lesion," "ulcerating lesion" and "annular lesion" were considered to be "accurate" diagnosis.

Ileum. There were 21 cases in which the tumor proved to be in this segment of the small intestine. Four were benign and 17 were malignant tumors. Fifteen of the cases were not considered to be pertinent to this analysis because in 3 of them no roentgenologic examination of any part of the gastrointestinal tract was made; in 8, roentgenologic examination of only the stomach or colon or both was carried out; and in 4, a clinically important lesion was correctly diagnosed roentgenologically in a part of the gastrointestinal tract other than the small intestine. This leaves but 6 cases (21 minus 15) for analysis. In 2 of the cases, 33 per cent, the lesion was overlooked; in 4, or 67 per cent, the lesion was recognized at the roentgenologic examination.

In our experience, then, the ileum seems to be the most difficult region of the small intestine from the standpoint of roentgenologic diagnosis. One of the lesions overlooked was, however, the small submucous hemangioma, 6 mm. in diameter, previously referred to, which was discovered in the pathologic examination of a resected specimen of ileocecal granuloma with persistent postoperative fecal fistula. Ordinarily this is not an error that would be charged against the roentgenologic examination, chiefly on account of its size and submucous situation. We expect, nevertheless, to encounter greater difficulty in the ileum, especially in that part of it adoral to its lowermost 12 inches (30 cm.) or so, chiefly because it is difficult to maintain a distending concentration of the contrast suspension there, and because these segments tend to seek such a low level in the pelvis that they are elevated from there often with greatest difficulty.

ROENTGENOLOGIC MANIFESTATIONS OF TUMORS OF THE SMALL INTESTINE

On several occasions we have described the manner of conducting the roentgenologic examination of the small intestine currently used in the Section on Roentgenology of the Mayo Clinic.[2,4] It is a technique which cannot be standardized precisely, because occasionally it must be changed in certain respects to suit individual cases. Briefly stated, the upper segments of the small intestine, the duodenum, the jejunum, and the upper two-thirds or so of the ileum are observed roentgenologically by following the progress of a simple mixture of equal parts of barium sulfate and water through these segments. In our experience the lowermost third of the ileum is usually studied to best advantage by filling it with contrast suspension in retrograde direction through the ileocecal orifice, roentgenoscopic and roentgenographic examinations being made after the bulk of the contrast material has been expelled from the colon. It is to be emphasized, however, that the roentgenoscopic examination is the cardinal roentgenologic maneuver, whether the contrast material has been administered orally or rectally, and in our opinion no number of interval roentgenograms made without reference to a competent roentgenoscopic examination could supplant it satisfactorily.

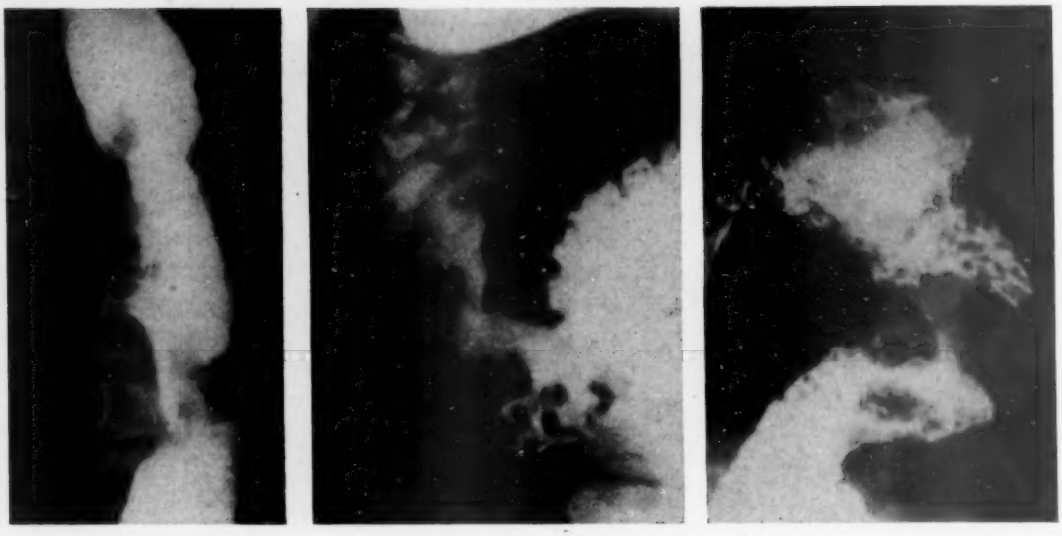

FIG. 1. Carcinoma of the esophagus (*left*), of the second portion of the duodenum (*center*), and of the sigmoid colon (*right*), for comparison. In each example are apparent (1) the abrupt demarcation between involved and uninvolved parts, (2) the complete absence of mucosal pattern in the filling defect, and (3) the eccentric, corrugated and tortuous channel produced by carcinoma.

Like the colon, the small intestine is a tubular organ. These divisions of the alimentary tract resemble each other in every important morphologic and physiologic respect. The pathologic processes which occur in them are similar, and both divisions are deformed by such processes in similar ways. Hence it is possible to apply the same roentgenologic criteria of diagnosis to the small intestine as have been found reliable in the diagnosis of the normal and abnormal large intestine.

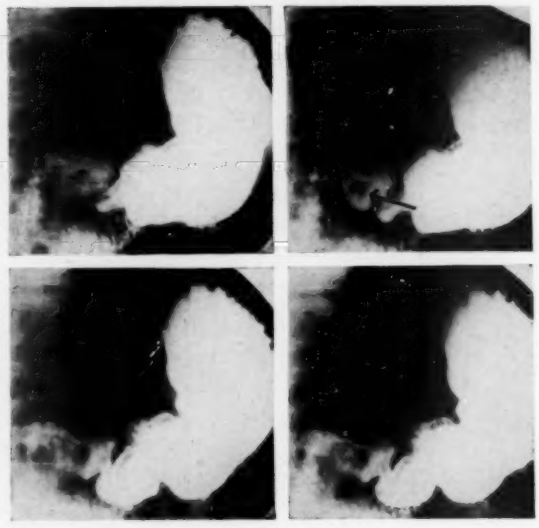

FIG. 2. The roentgenologic appearance that a polypoid lesion of the duodenum would assume. This rounded "central" filling defect (arrow) was caused, however, by a pancreatic nodule impinging on the lumen of the duodenum from without.

Pathologic processes deform the tubular segments and it is chiefly by the roentgenologic demonstration of such deformities that the presence of disease is determined. One type of pathologic process is distinguished from others by analysis of the morphologic features of the deformity produced and by interpretation of them in terms of pathologic anatomy. The term "deformity" includes the concept of that familiar term in roentgenologic literature, the "filling defect," which may be defined as a subtraction from the normal luminal outline, and the concept antithetic to this, namely, an addition to the normal luminal outline, of which the diverticulum and the penetrating ulcer are most familiar examples. Tumors, both benign and malignant, deform all segments of the alimentary tract, especially the simple tubular ones, like the esophagus, small intestine and colon, in a way peculiar to themselves (Fig. 1). The deformity pro-

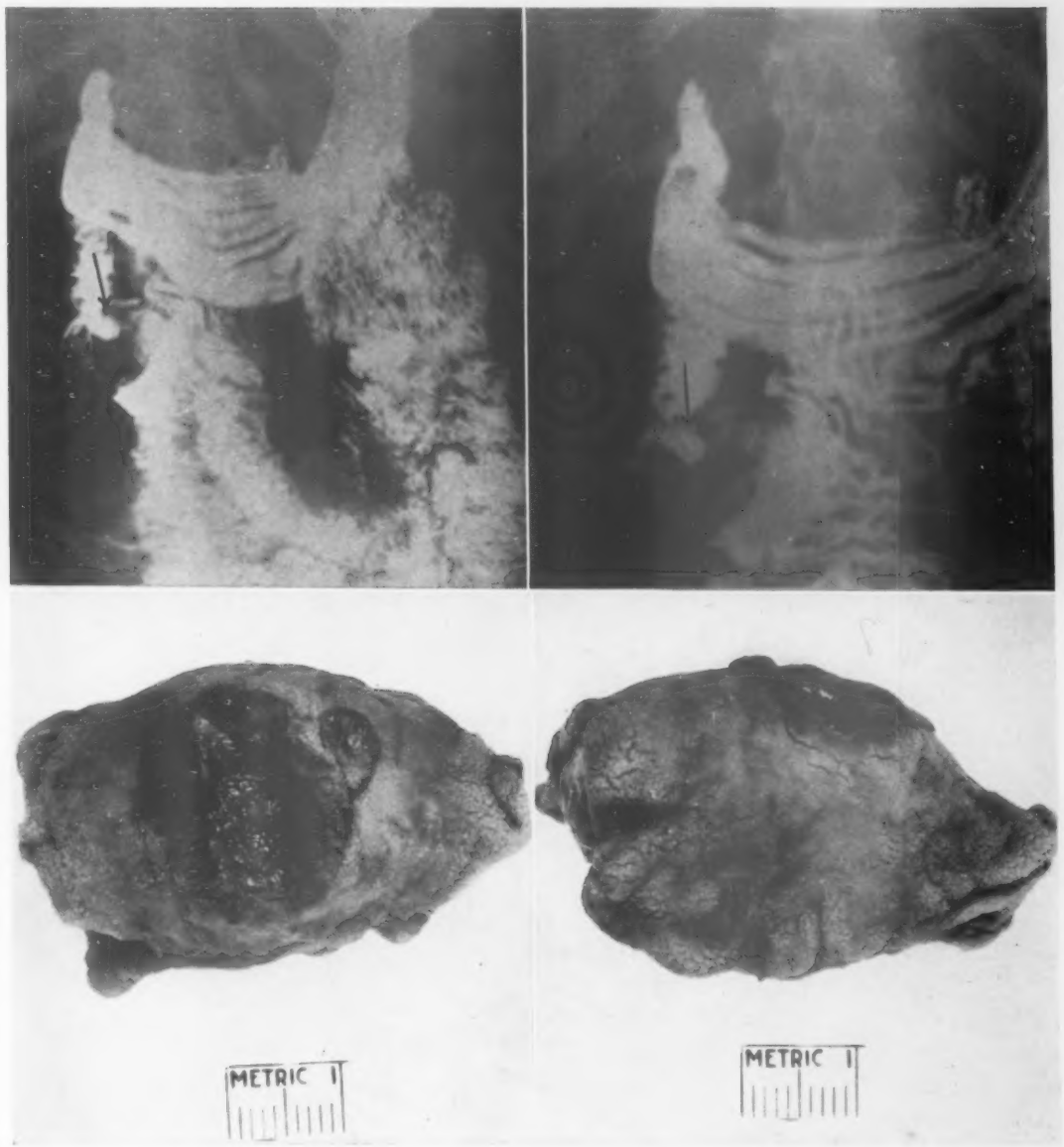

Fig. 3. Leiomyosarcoma of the second portion of the duodenum. The lesion was actually in the wall of the duodenum, but had ulcerated into the lumen. The mucosal folds over the tumor and surrounding the ulcer (arrows) were flattened out. The specimen was removed surgically.

duced by a tumor may be marginal or encircling, in whole on in part, such as the one produced by an annular carcinoma, or it may be internal or central, such as is produced by the lesions known as polyps or polypoid lesions (Fig. 2). In any case, the "filling defect" produced by tumors not complicated by perforation is relatively short and is sharply demarcated aborally and adorally, and the mucosal pattern throughout the extent of the defect is obliterated.

Tumors arising in the submucous structures frequently do not actually invade and destroy the mucous membrane over them, but when they become large enough to be recognized roentgenologically, they obliterate the mucosal pattern over them if in

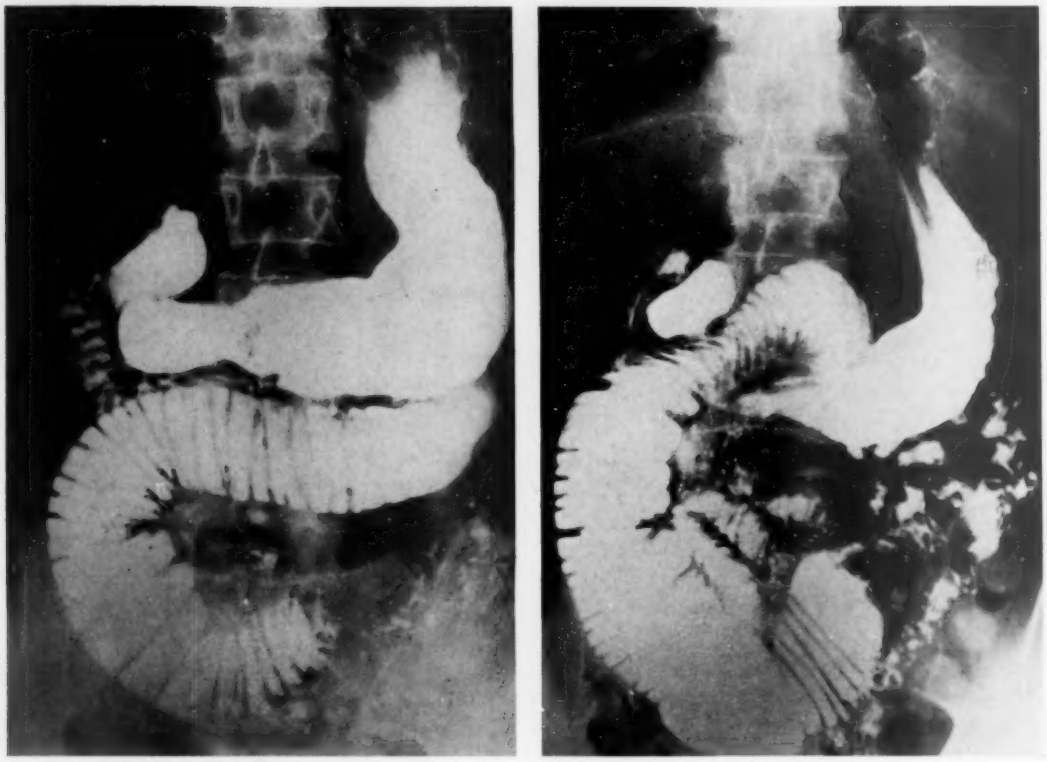

FIG. 4. Obstructing adenocarcinoma high in the jejunum. The roentgenograms show only the obstructive phenomena. At roentgenoscopic examination, however, the filling defect could be seen to better advantage, permitting the diagnosis of carcinoma to be made.

no other way than by stretching the mucous membrane to the point of obliterating its folds, the basis for the mucosal pattern (Fig. 3). Often tumors of the colon and small intestine produce obstruction of such degree that the morphologic features of the lesion are not manifested roentgenologically. In such instances it may be impossible to render a more specific roentgenologic diagnosis than that of obstructing lesion (Fig. 4). A similar situation develops in case of intussusception whether it be entero-enteral, enterocolic or colocolic. In adults primary intussusception is so rarely encountered that for practical purposes it can be said that the condition is not seen except with tumor as its cause (Fig. 5).

Tumors and other lesions of organs contiguous to or very near the small intestine may extend to it and involve it segmentally, producing a roentgenologic picture similar in many respects to that produced by primary intestinal tumors. Lesions, especially cysts and tumors, of the pancreas seem particularly prone to do this (Fig. 6). The roentgenologic evidence of the essentially extra-enteral nature of the process is usually elicited at the roentgenoscopic examination. Such extrinsic lesions are usually large and thus careful palpation under roentgenoscopic control will almost always yield the key to the correct diagnosis.

These are the cardinal signs from which the roentgenologic examiner derives the concept of tumor, using that term here, as elsewhere in this paper, in its narrower sense to signify blastoma, as distinguished from inflammatory tumors or granulomatous processes. These signs must be understood to be but gross morphologic evidences, and thus it is impossible, as a rule, to derive from them reliable concepts regarding the histopathologic nature of the tumor, such as its malignancy or nonmalig-

nancy, and the histologic type of tissue of which it is composed.

The rule may be stated that there are no reliable roentgenologic evidences of benignancy once the evidence for tumor is produced. True enough, certain lesions are well circumscribed, regular in contour, and soft in consistency, and show no gross evidence of tendency to invade; in other words, they may manifest all the so-called classical gross morphologic evidences of benign tumors. At the present time, however, it has become well understood and universally accepted that such lesions may in fact, on microscopic examination, prove to be true malignant lesions. This holds particularly true for such tumors when they are found in the gastrointestinal tract. The roentgenologic examiner, then, since he is dealing with gross morphologic characters of lesions, rarely if ever can elicit diagnostic data on which he can guarantee the benignancy of a tumor he has discovered. He may say that the lesion he has found "looks," like a benign lesion to him, and his opinion may later be proved correct in most instances, but his medical and surgical consultants had best not consider his diagnostic guess too seriously, but prefer to consider the morphologic features he described and treat the lesion as a malignant one until competent histologic study proves its true nature.

Lesions that are not tumors deform the tubular segments of the intestinal tract in a different way.[3] As a group they tend to extend over longer segments, producing longer deformities. Demarcation between involved and uninvolved segments is gradual, not abrupt. Depending on the patho-

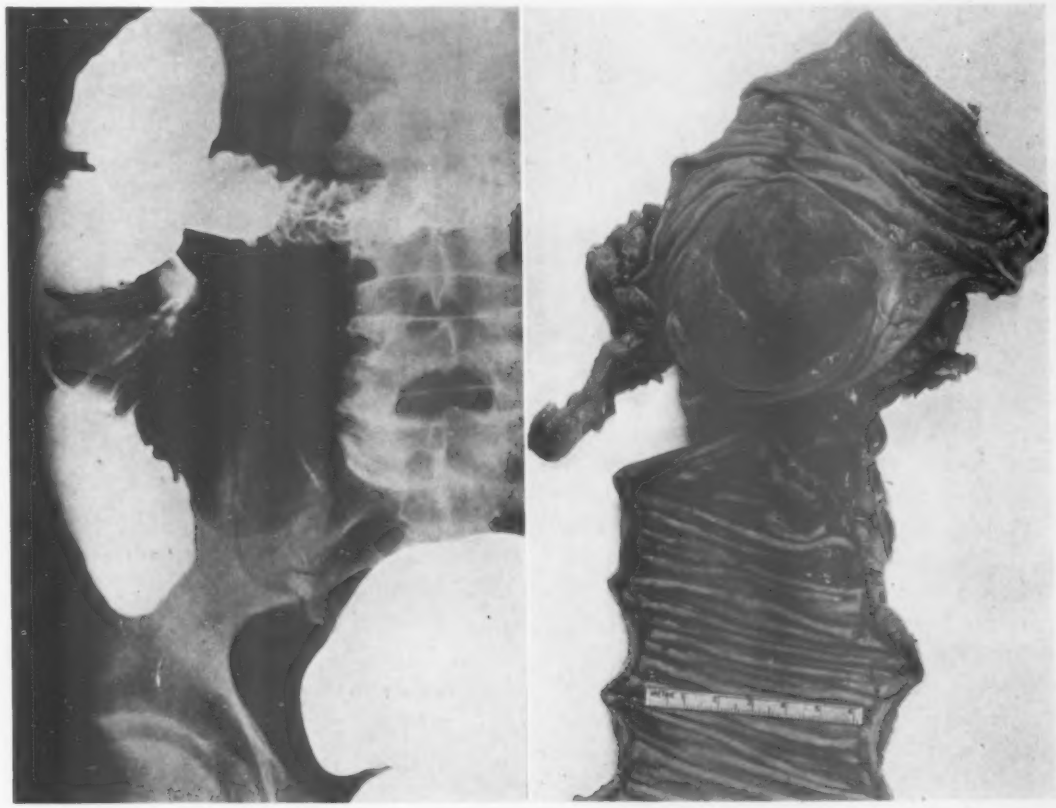

FIG. 5. Ileocolic intussusception. The lesion causing this was a sarcoma collaring the lowermost portion of the ileum 2 inches (5 cm.) above the ileocecal junction. The roentgenogram was made after the opaque enema had been evacuated from the colon. The specimen was removed surgically.

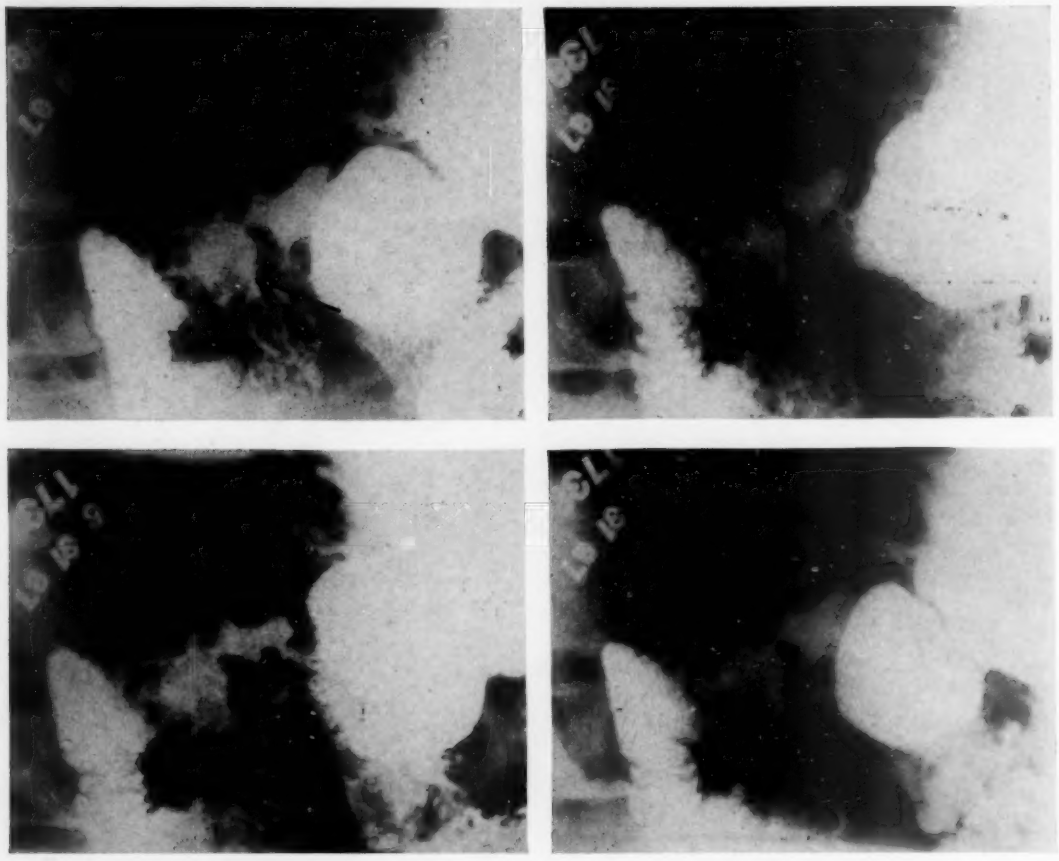

FIG. 6. Carcinoma of the head of the pancreas producing trophic ulceration (arrow) into the second portion of the duodenum.

logic nature and severity of the disease producing the deformity, the mucous membrane may or may not be destroyed, and the mucosal pattern is correspondingly altered. Even when the mucosal pattern is obliterated completely by ulceration, however, the mucosal relief has a different roentgenologic appearance than the relief pattern of tumors has. The experienced roentgenologic examiner recognizes a typical mucosal relief pattern associated with tumors, and especially with malignant tumors. He makes use of his familiarity with this pattern in instances in which a malignant tumor has perforated. In this event the lesion takes many of the morphologic characteristics of the inflammatory, tumefactive processes, and it is only by eliciting what may be called the typical mucosal relief pattern of malignant tumor that the roentgenologic examiner can arrive at a diagnosis of the true nature of such lesions.

We have endeavored by a statistical study of the cases of tumor of the small intestine that have come under our observation to show that the roentgenologic examination has a very real contribution to make to the diagnosis of lesions of the small intestine. It is true that the roentgenologic examination of this division of the alimentary tract has not approached the efficiency of the roentgenologic method applied to the divisions above and below it. Such efficiency perhaps is too much to hope for. Certain it is, however, that with accumulating experience improvement will come. Our clinical

and surgical consultants have given evidence of greater interest in this examination and of greater reliance on it. Thus we think more lesions will be discovered. Accumulating clinical experience will eventually lead to a better selection of cases for roentgenologic examination, and thus many a patient will gain the advantage of earlier treatment than at present for these otherwise, for the most part, hopeless conditions.

REFERENCES

1. Mayo, C. W. Malignancy of the small intestine. *West. J. Surg.*, 1940, *48*, 403–407.
2. Weber, H. M. Discussion. *Proc. Staff Meet., Mayo Clin.*, 1936, *11*, 718–720.
3. Weber, H. M. Roentgenologic manifestations of non-neoplastic lesions of the small intestine. *J. Am. M. Ass.*, 1939, *113*, 1541–1546.
4. Weber, H. M., and Kirklin, B. R. Roentgenologic investigation of the small intestine. *M. Clin. North America*, 1938, *22*, 1059–1072.

HEMORRHAGE FROM GASTRITIS

A REPORT BASED ON PATHOLOGICAL, CLINICAL, ROENTGENOLOGICAL AND GASTROSCOPIC FINDINGS*

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IN a previous paper[1] I have emphasized the importance of bleeding from gastritis. In that report it was concluded that varying degrees of hemorrhage from chronic gastritis may take place in the absence of other demonstrable pathology in the gastrointestinal tract. Further observation has confirmed that opinion.

The subject of hemorrhage from gastritis is not a new one but is one which had received little consideration in this country until the development of the Wolf-Schindler flexible gastroscope. Among the earlier authors who have written on this subject should be mentioned Langerhans,[7] Nauwerck,[10] Einhorn,[2] Pariser[11,12], and Mintz.[8] Recent writers include Faber,[3] Schindler,[14,15] Schindler, *et al.*,[16,17] Moutier,[9] Korbsch,[6] and Henning.[4] Faber considers severe hemorrhage to be a frequent symptom in gastritis. Schindler, Ortmayer and Renshaw[17] have pointed out that "gross, sometimes fatal, hemorrhages from gastritis have occurred."

In the following pages the evidence for bleeding from gastritis will be considered from the pathological, clinical, roentgenological and gastroscopic standpoints.

PATHOLOGICAL MATERIAL

Necropsy Evidence. In Table I are listed 3 cases known clinically to have had hematemesis. Death occurred from other causes but the hematemesis was explained by the finding of gastritis at autopsy. In 2 of these cases there was marked injection of the gastric mucosa and in one there was 300 cc. of blood in the stomach at autopsy. In one case the esophagus and duodenum were also involved in the inflammatory process, but in none of the cases was there any ulcer, neoplasm, varix or possible source of hemorrhage other than the gastritis.

TABLE I

DEMONSTRATING 3 CASES OF HEMATEMESIS SHOWN AT AUTOPSY TO HAVE CHRONIC GASTRITIS AS THE ONLY SOURCE OF THE HEMORRHAGE

Necropsy No.	Age	Sex	Clinical Diagnosis	Autopsy Findings in Stomach	Pathological Diagnosis
8867	77	M	Congestive failure	Lack of normal rugae	Atrophic gastritis
8427	48	F	Cholecystectomy Acute pancreatitis	Marked injection with capillary dilatation	Acute esophagitis Acute gastroduodenitis
6682	74	F	Diaphragmatic hernia Hypertensive heart disease	300 cc. blood. Diffuse mucosal injection	Chronic gastritis

In Table II are listed 7 cases with no history of gastrointestinal bleeding but with definite evidence at autopsy of bleeding from gastritis. In all of these blood was found in the stomach and in all of them a pathological diagnosis of gastritis was made. In 5 cases gastritis was the only demonstrable source of the hemorrhage. In one a healed duodenal ulcer was found and

* From the Massachusetts General Hospital. Read at the Forty-first Annual Meeting, American Roentgen Ray Society, Boston, Mass., Oct. 1–4, 1940.

in another a duodenal ulcer almost healed. In both of these bloody fluid was found in the stomach. Since it is difficult to conceive how bloody fluid could occur in the stomach from a healed ulcer of the duodenum, one must conclude that the hemorrhage in that case came from an inflamed gastric mucosa. In the case of the almost healed duodenal ulcer there were found at autopsy numerous small petechial hemorrhages and the stomach was found partially filled with black coffee-ground material. Since no blood was found in the duodenum the presumption is that the bleeding came solely from the gastritis. This raises the very important question as to whether, in the presence of a roentgen diagnosis of peptic ulcer and a gastroscopic diagnosis of gastritis with hemorrhage, the bleeding is coming from the ulcer or from the gastritis or from both. Presumably the answer is that in some of these cases the bleeding is coming from the ulcer, in others from the gastritis, while in many it is coming from both. In clinical cases with hematemesis and a gastroscopic report of gastritis with active bleeding how much emphasis should be placed on a roentgen report of "duodenal deformity with no crater," "healed duodenal ulcer," etc.? The chief source of the bleeding in these cases may well be the gastritis.

TABLE II

DEMONSTRATING 7 CASES WITHOUT CLINICAL HISTORY OF BLEEDING BUT WITH POSITIVE PATHOLOGICAL EVIDENCE OF BLEEDING FROM GASTRITIS

Necropsy No.	Age	Sex	Clinical Diagnosis	Autopsy Findings in Stomach	Pathological Diagnosis
7105	54	M	Hypertensive heart disease	Bloody fluid ++++ Mucosa injected Purpuric spots	Gastritis
7135	20	F	Diabetes	Bloody mucus + Mucosa injected. Few small superficial ulcerations	Acute gastritis
7259	45	M	Congestive failure	Bloody fluid +++ Multiple submucous hemorrhagic areas	Gastritis
8305	56	M	Lysis of posterior gastroenterostomy for jejunal ulcer. Gastroduodenostomy	Bloody fluid +++ Mucosa deep red. Markedly injected	Acute hemorrhagic gastritis
8766	47	F	Cancer of the colon Postoperative shock	Many black petechial hemorrhages	Chronic gastritis
7001	58	F	Cancer of the bladder	Bloody fluid ++++	Gastritis. Healed duodenal ulcer
5991	60	F	General peritonitis	Bloody fluid Numerous small petechial hemorrhages	Hemorrhagic gastritis Duodenal ulcer (almost healed)

Further incontrovertible evidence of hemorrhage from gastritis is given in the following brief case report of fatal bleeding from acute alcoholic gastritis.

CASE 1 (M. G. H. #309502). A Swedish male, aged forty-nine, storekeeper, entered the hos-

TABLE III

THREE CASES OF SEVERE HEMORRHAGE FROM GASTRITIS NECESSITATING GASTRIC RESECTION DIAGNOSIS SUGGESTED ROENTGENOLOGICALLY, ESTABLISHED GASTROSCOPICALLY, AND CONFIRMED HISTOLOGICALLY

Hospital No.	Age	Sex	Previous Gastric Operation	Hematemesis	Melena	Roentgen Findings	Present Gastric Operation	Pathological Report	Follow-Up
P.H. U No. 1312	45	M	Pylorectomy Posterior gastroenterostomy	0	+++	Some evidence of gastritis	Partial gastrectomy	Subacute and chronic gastritis	No further bleeding 20 mo. postoperative
U No. 30620	35	M	Billroth II	++++	+++	Markedly enlarged folds Hypertrophic gastritis	Subtotal gastrectomy	4 mm. erosion severe gastritis	Patient still in hospital
M.G.H. No. 251615	51	F	0	++++	++++	Prominent rugae	Partial gastrectomy	Chronic gastritis	Died postoperative pneumonia

pital August 9, 1931, in a semi-comatose condition. The only history obtainable was that he had felt well until about two weeks ago when he began drinking bay rum and rubbing alcohol in considerable amounts.

Three days prior to admission he vomited coffee-ground material on several occasions after which he discontinued any further use of alcohol and continued to feel quite well. On admission to the Emergency Ward he would barely respond to questions and was believed to be in a state of shock from hemorrhage.

Inasmuch as there had been a questionable roentgen diagnosis of duodenal ulcer one year previously it was felt that hemorrhage on the present admission probably came from a duodenal ulcer. In spite of transfusion the blood pressure fell rapidly and the patient died five hours after admission.

Postmortem examination showed the stomach to be filled with thin grayish-black fluid. There were multiple erosions and ecchymoses in the gastric mucosa. Healed duodenal ulcers were also noted.

Comment. In this case there can be no doubt that the cause of death was hemorrhage from acute alcoholic gastritis. Healed duodenal ulcers were found but could not explain the bleeding. Here again is pathological evidence that, even with a positive roentgen diagnosis of duodenal ulcer in the past, the present episode of massive fatal hemorrhage was from gastritis.

Surgical-Pathological Evidence. In Table III are listed the summaries of 3 patients who have undergone gastric resection because of severe hemorrhage from gastritis. In none of these was any other pathologic condition demonstrable that would account for the bleeding. Two of them had had a previous gastric operation. All resected specimens showed chronic gastritis on microscopic examination. We thus have every evidence clinically and pathologically that the hemorrhage occurred from chronic gastritis.

Since gastric surgery is so rarely necessary in chronic gastritis even with hemorrhage it seems pertinent to report in detail the following case of postoperative gastritis where repeated hemorrhage finally led to subtotal gastrectomy.

CASE II. (M. G. H. U#30620) J. E. K., male, single, unemployed, aged thirty-five, entered the hospital for the *ninth* time on August 27, 1940, because of gastrointestinal hemorrhage.

Past History. In 1921 at the age of sixteen a posterior gastroenterostomy was done at an-

other hospital, apparently for bleeding duodenal ulcer.

First admission, 1934. Severe hematemesis. Pylorectomy. No ulcer found.

Second admission, 1935 (June). Severe hematemesis and melena. Red blood cells 1.5 million. Transfused twice. Gastroscopy showed superficial gastritis with erosion.

Third admission, 1935 (November). Severe hematemesis and melena. Red blood cells 1.8 million.

Fourth admission, 1937 (March). Severe hematemesis and melena. Red blood cells 1.1 million. Recent bronchopneumonia. Gastrointestinal series showed marked swelling of the rugae about the stoma (Fig. 1). No ulcer demonstrable. Gastroscopy showed marked hypertrophic gastritis with erosions, similar to that shown in Figure 2.

Fifth admission, 1937 (September). Severe hemorrhage. Red blood cells 1.8 million.

Sixth admission, 1938 (January). Moderate melena after many hours of shovelling snow. Red blood cells 3.0 million.

Seventh admission, 1938 (May). Moderate melena. Red blood cells 2.6 million. Gastroscopy showed improvement, slight superficial and hypertrophic gastritis. Roentgen examination showed no definite evidence of swelling of the rugae. No ulcer crater demonstrable. Special roentgen studies of the small intestine were negative.

Eighth admission, 1940 (January). Severe hematemesis and melena. Red blood cells 2.0 million. Roentgen examination showed widening of the folds. Gastritis, no evidence of jejunal ulcer. Gastroscopy showed superficial and hypertrophic gastritis with multiple erosions, superficial ulcerations and hemorrhage.

Fig. 1. Case 11. Roentgen appearance showing marked widening of the gastric rugae. Diagnosis: chronic gastritis.

Fig. 2. Case 11. Gastroscopic appearance of severe postoperative gastritis with multiple erosions and hemorrhage. Resection was performed with complete relief. Pathological report: chronic gastritis. (Reproduced by courtesy of the *New England Journal of Medicine*, 1940, *222*, 427–434.)

Ninth admission, 1940 (August). Moderate melena. Red blood cells 3.6 to 4.9 million after transfusion. Operation, subtotal gastrectomy, with two transfusions. Convalescence uneventful. Pathological report—mucosa red and injected, rugae prominent. One centimeter from the posterior gastroenterostomy stoma is a small punched out erosion 4 mm. in diameter. Diagnosis—chronic gastritis (Fig. 3).

Comment. This case is reported to show multiple episodes of massive hemorrhage with repeated roentgen and gastroscopic examinations revealing severe gastritis but no other pathologic condition. Subtotal gastric resection was finally performed and pathological examination confirmed the diagnosis of severe gastritis with erosion. No other pathologic condition was found.

CLINICAL MATERIAL

Turning now to the clinical material, we find naturally enough that in the pre-gastroscopic period the diagnosis of gastritis with hemorrhage was very rare. Four such

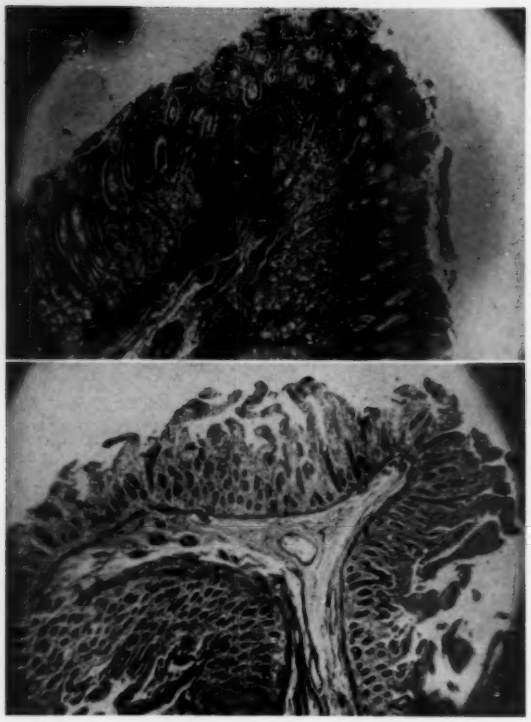

Fig. 3. Case 11. Microscopic appearance of resected specimen. Note marked leukocytic infiltration and capillary engorgement close to mucosal surface.

cases, however, have been found in the records and are listed in Table IV. It will be seen that in all of them there was hematemesis, in 2 there was an alcoholic history, in one roentgen examination showed prominent rugae and in this same case later resection showed chronic gastritis histologically. Thus, in 3 cases the diagnosis is presumptive, in the fourth suggested by roentgen examination and proved at operation.

Since 1933 when we began the frequent use of the flexible gastroscope at this hospital the diagnosis of hemorrhage from gastritis has been made in 42 cases. Since gastroscopy has shown chronic gastritis without other pathologic condition in 213 cases during this period, the incidence of hemorrhage in gastritis is 19.7 per cent. In Tables V and VI are listed 42 cases of chronic gastritis with hemorrhage. There was mild bleeding in 7, moderate bleeding in 14 and severe bleeding in 21 cases. Presumably patients who bleed only slightly or moderately come to the hospital less frequently for thorough study, for there are in this series as many cases with severe bleeding as with mild and moderate bleeding together. A positive diagnosis of gastritis was made by gastroscopy in all cases. Although a positive roentgen diagnosis of gastritis was made in only 3 cases, in 6 others the roentgenologist reported widening or hypertrophy of the rugae. Such a finding alone is insufficient for a positive diagnosis of gas-

Table V

TO SHOW THE DEGREE OF HEMORRHAGE AND ROENTGEN FINDINGS IN 42 CASES OF BLEEDING FROM GASTRITIS DIAGNOSED BY GASTROSCOPY

Degree of Hemorrhage	Roentgenogram Negative	Roentgenogram Suggestive of Gastritis	Total
Mild	6	1	7
Moderate	11	3	14
Severe	16	5	21
			42*

* Gastric or duodenal diverticula by roentgen examination in 6 cases.

Table IV

CLINICAL CASES
PRE-GASTROSCOPIC PERIOD

Hospital No.	Age	Sex	Alcohol	Hematemesis	Roentgen Findings	Clinical Diagnosis
295706	30	M	+++	+	Negative	? Gastritis
324886	42	M	++	+++	Negative	? Acute gastritis
266281	21	M	0	+++	None	Acute gastritis
251615	51	F	0	++++	Prominent rugae	Chronic gastritis

TABLE VI

GASTROSCOPIC CLASSIFICATION OF 42 CASES OF GASTRITIS WITH HEMORRHAGE

Degree of Hemorrhage	Superficial	Hypertrophic	Atrophic	Postoperative	Mixed	Total
Mild	3	2	0	0	2	7
Moderate	3	4	1	2	4	14
Severe	7	6	1	3	4	21
	13	12	2	5	10	42

tritis, for as Schatzki[13] has pointed out, the roentgen diagnosis of hypertrophic gastritis depends in principle on demonstrating widening of the rugae, increased rigidity of the rugae and increased secretion of mucus. With these criteria a positive roentgenological diagnosis of hypertrophic gastritis is of significance and is usually confirmed gastroscopically, though I have seen such cases with a positive roentgen diagnosis of hypertrophic gastritis where gastroscopy showed a normal appearing mucosa or only slight superficial gastritis. Roentgenologists and gastroscopists are generally agreed that a negative roentgen examination is of no value in excluding gastritis, for in the presence of a negative roentgen report gastroscopy frequently demonstrates important changes in the gastric mucosa, namely inflammation, erosions, superficial ulcerations, atrophic and hypertrophic changes. The very superficial character of the erosions or ulcerations seen by gastroscopy makes them particularly difficult to demonstrate roentgenologically. Henning and Schatzki,[5] however, have reported a case with multiple erosions shown by roentgen examination, admitting that their demonstration is very unusual and difficult. In Table VI it will be seen that many of the cases of hemorrhage from gastritis are classified gastroscopically as belonging to the superficial, atrophic, postoperative or mixed groups. Atrophic gastritis is not demonstrable by roentgen examination. Superficial, postoperative, or mixed groups may be suggested roentgenologically but for positive confirmation and classification such cases should be studied by gastroscopy. In the 42 cases tabulated in Tables V and VI all other possible sources of hemorrhage were excluded by roentgen examination, except gastric or duodenal diverticula in 6 cases. Diverticula in these locations, however, are not usually considered to be a cause of hemorrhage. A positive gastroscopic diagnosis of gastritis in a patient with otherwise unexplained hematemesis or melena is therefore of great importance.

Other aspects of the problem of bleeding from gastritis must be considered. Two cases have been observed gastroscopically with no history of hematemesis or melena and yet the gastric mucosa appeared inflamed and friable and was observed to bleed easily when touched with the tip of the gastroscope. Since normal gastric mucosa does not bleed during gastroscopic examination such cases may be classed as potential and perhaps subclinical bleeders from gastritis. The converse is also true, that is 4 cases of hematemesis have been observed where both roentgen and gastroscopic examinations have been entirely negative and no source for the bleeding could be determined. This observation raises the important question as to the rapidity of healing of erosions and ulcerations. In my opinion erosions and superficial ulcerations may heal in a few days and even true peptic ulcer demonstrable roentgenologically may heal in a week. Since roentgen and gastroscopic examinations are often delayed for many days or weeks after the bleeding it is not surprising that its true source may not be determined. A striking example of the apparent rapid healing of a peptic ulcer has recently come to my atten-

tion in a patient shown by roentgen examination to have an active duodenal ulcer, yet fourteen days later operation with duodenotomy showed no ulcer. An extraordinary feature of this case was that sixteen days after the operation active duodenal ulcer was again demonstrated roentgenologically! Both the roentgenologist and the surgeon were very well trained observers.

Perhaps the most interesting phase of this entire discussion is the question as to whether in a case with both ulcer and gastritis the bleeding is coming from the ulcer or from the gastritis or from both. This question has already been considered in this paper under the pathological evidence but may be further elaborated. Certainly we have overwhelming evidence of the fact that hemorrhage may come from peptic ulcer, and we also have undeniable evidence that bleeding may come from gastritis. In addition to the 42 cases reported above as bleeding from gastritis with no other demonstrable pathology, there are records here of 24 cases with gastritis and hemorrhage in which the question of ulcer was also raised. In 5 of these there was roentgen evidence of a healed duodenal ulcer at the time of the hemorrhage (4 cases) or subsequently (1 case). Presumably these cases bled from gastritis alone, for as already remarked, bleeding does not occur from a healed ulcer. In 9 cases there was reported from the roentgen examination a duodenal deformity without crater or a question of duodenal ulcer either on a previous examination (3 cases), at the present examination (4 cases) or at a subsequent time (2 cases). It is difficult to see how present bleeding can be explained by a questionable ulcer at a previous or subsequent roentgen examination. Even a duodenal deformity without crater at the time of the bleeding is not positive proof that the bleeding came from the duodenum rather than from the gastritis demonstrated by gastroscopy. In 10 cases there was a positive roentgen diagnosis of duodenal or gastric ulcer at the time of the bleeding. Since there was gastroscopic evidence of gastritis in all of these cases it is still more than likely that at least some of the hemorrhage was from the gastritis. To aid in settling this question more cases must be studied roentgenologically and gastroscopically within a very few days of the hemorrhage.

In addition to the above 66 cases of gastritis with hemorrhage there are a few other cases to be considered. Four cases of hiatus hernia with bleeding have been examined by gastroscopy or by esophagoscopy and all have been found to have a gastritis in the region of the hernia. It is believed that the gastritis in these cases is the underlying cause of the hemorrhage. In one case of gastric varices, one of scurvy, one of chronic thrombocytopenic purpura and one of familial hemorrhagic telangiectases, all with hematemesis or melena, chronic gastritis was demonstrated by gastroscopy.

CONCLUSIONS

Proof is offered from autopsy and surgical material that severe, even fatal hemorrhage may occur from gastritis alone in the absence of other demonstrable pathologic condition.

Gastroscopic evidence of gastritis as the only source of bleeding is presented in 42 clinical cases.

Gastroscopic evidence of gastritis as a possible source of hemorrhage is presented in 24 additional clinical cases with ulcer or with questionable ulcer.

Bleeding may occur from superficial, atrophic, hypertrophic or postoperative gastritis. Bleeding occurred in 42 out of the 213 cases of gastritis studied during this period, or an incidence of 19.7 per cent.

Roentgen examination suggested gastritis in 9 of the 42 bleeding cases reported, or an incidence of 21.4 per cent.

REFERENCES

1. BENEDICT, E. B. Hemorrhage from gastritis—gastroscopic study. *Am. J. Digest. Dis. & Nutrition*, 1937, *4*, 657–664.
2. EINHORN, M. Ein klinischer Beitrag zur Kenntniss und Behandlung der Erosionen des Magens. *Berl. klin. Wchnschr.*, 1895, *32*, 457.

3. Faber, K. Gastritis and Its Consequences. Oxford Medical Publications, New York and London, 1935, p. 73.
4. Henning, N. Die Entzündung des Magens. J. A. Barth, Leipzig, 1934, p. 87.
5. Henning, N., and Schatzki, R. Gastrophotographisches und röntgenologisches Bild der Gastritis ulcerosa. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1933, *48*, 177–182.
6. Korbsch, R. Ueber Hämatemesis bei chronischer Gastritis. *München. med. Wchnschr.*, 1925, *72*, 1558.
7. Langerhans, R. Ungewöhnliche Art der hämorrhagischen Erosion des Magens. *Virchow's Arch. f. path. Anat.*, 1891, *124*, 373.
8. Mintz, S. Ueber hämorrhagische Magenerosionen. *Ztschr. f. klin. Med.*, 1902, *46*, 115.
9. Moutier, F. Traité de gastroscopie et de pathologie endoscopique de l'estomac. Masson et Cie, Paris, 1935, p. 140.
10. Nauwerck, C. Gastritis ulcerosa chronica. *München. med. Wchnschr.*, 1897, *44*, 955.
11. Pariser, C. Ueber hämorrhagische Erosionen der Magenschleimhaut. *Med. Rev. Wien.*, 1897, No. 3.
12. Pariser, C. Ueber hämorrhagische Erosionen der Magenschleimhaut. *Berl. klin. Wchnschr.*, 1900, *37*, 954.
13. Schatzki, R. Comparative value of gastroscopy and roentgen examination of the stomach. *Radiology*, 1937, *29*, 488–491.
14. Schindler, R. Die diagnostische Bedeutung der Gastroskopie. *München. med. Wchnschr.*, 1922, *15*, 535.
15. Schindler, R. Observations gastroscopiques sur la gastrite chronique. *Arch. d. mal. de l'app. digestif*, 1931, *21*, 680–685.
16. Schindler, R., and Ortmayer, M. Classification of chronic gastritis with special reference to gastroscopic method. *Arch. Int. Med.*, 1936, *57*, 959–978.
17. Schindler, R., Ortmayer, M., and Renshaw, J. F. Chronic gastritis. *J. Am. M. Ass.*, 1937, *108*, 465–468.

THE DIAGNOSIS OF GASTRIC CANCER

AN ANALYSIS OF THE GASTROSCOPIC AND ROENTGENOLOGIC FINDINGS

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THE early diagnosis of gastric cancer is best accomplished by using methods giving visual evidence of pathology, as the clinical picture is often vague and poorly defined.[9] Gastroscopy and roentgenology are available for the direct preoperative study of the mucosa and the deeper layers of the stomach. In determining the relation between gastroscopy and roentgenology in the diagnosis of gastric cancer, two questions are involved: (1) How many lesions are visualized by one method and not by the other, and (2) how often is the differentiation between benign and malignant lesions correctly made by one and not by the other?

The material used in answering these two questions consists of 189 cases selected from 1,072 patients examined by both gastroscopy and roentgenology. These 189 cases include not only all of the polypoid, ulcerating and infiltrating cancers but also the benign counterparts—namely, polyps, ulcers and certain forms of gastritis. In 74 cases the character of the lesions was proved by microscopic study of the specimens, most of which were obtained by surgery. The majority of the other cases were followed sufficiently long so that their true nature seems assured. The latter group is included in order to obtain a clearer conception of the relation existing between gastroscopy and roentgenology, since the indications for surgery depend largely on gastroscopic and roentgenologic findings.

The discrepancies that occur between the findings of a gastroscopist and those of a roentgenologist, aside from inherent differences in the two diagnostic methods, vary according to the examiners' experience, dexterity and opinions. Much of the work was done when gastroscopy, as performed with the flexible instrument, was in its infancy and the roentgenologist was familiarizing himself with the relief and compression techniques. In the process of learning, difficulties were encountered and mistakes were made which are not repeated today. As time continues, improvements in technique and interpretation should further decrease the number of errors.

Although all of the figures here presented are based on first examinations, the importance of either the roentgenologist or the gastroscopist having knowledge of the other's findings must not be overlooked. It often happens that the nebulous findings of one examiner are definitely confirmed by the other, once the suspected location is known. The explanation for this is found in the fact that certain maneuvers and positions ordinarily omitted in the course of a routine examination are used.

In view of these factors, our purpose, then, is not to establish a relative efficiency of one method over the other but is to show that the accuracy of diagnoses obtained by using both methods is greater than that obtained by using only one.

VISUALIZATION OF LESIONS

Polypoid Lesions

In 16 patients the gastroscopist at his first examination reported polyp. The roentgenologist confirmed this diagnosis in only 4. This discrepancy, similar to that of other observers,[13,20], is used to support the argument that gastroscopy is superior to roentgenology in demonstrating small neoplasms.[8,14] We are by no means convinced that this superiority exists, even though only one patient underwent pathologic

examination. For one thing, the gastroscopist does not always confirm his original observations by further gastroscopic examination. Eight of the 16 patients were re-examined by the gastroscopist and in 3 the presence of polyps was not confirmed. In the other 5 patients the gastroscopist reaffirmed his original diagnosis of polyp in 4 and partially changed his opinion in the fifth at subsequent examination. The 4 cases in which the gastroscopist confirmed the diagnosis of polyp were the same 4 in which the roentgenologist found polyp. In 1 of these 4 cases the roentgenologist saw the polyp at the second examination, after the location was pointed out by the gastroscopist. In the fifth patient the roentgenologist reported the stomach as "normal" before and after the gastroscopist reported "polyps." The gastroscopist was unable to differentiate between polyps, hyperplasia and chronic gastritis at a second examination.

In a group of 5 cases not studied pathologically and reported by the gastroscopist as having smooth, poorly defined, hemispherical protrusions not flattened by the introduction of air, the roentgenologist described a normal stomach in 4. Two of these 4 patients were re-examined by the gastroscopist and in neither were the findings reaffirmed. In the fifth, stiffened rugae, localized to the region in which the gastroscopist described changes on two occasions, were observed at roentgen examination. The gastroscopist usually spoke of a fibroma or a myoma. Flexner and Fleishman[6] mention 3 similar cases, not proved by pathologic examination.

None of the polypoid carcinomas seen by the roentgenologist underwent gastroscopic examination.

The fact that the gastroscopist reaffirmed his original observations in only half of the cases subjected to re-examination indicates that he, like the roentgenologist, is apt to mistake certain transient rugal forms as polyps. Schindler[16] admits this possibility but believes that re-defining of the criteria for the diagnosis of polyps and the better visualization given by the newer instruments will decrease the discrepancy which exists between one gastroscopic observation and the next. He does not believe a mistake in identification can be made if the polyps lie on the foldless mucosa of an atrophic gastritis.

Ulcerating Lesions

In 123 benign and malignant ulcers, 33 of which were proved by pathologic studies and 58 by the clinical criteria described by Palmer,[12] 22 benign and 2 malignant ulcers were not seen by the gastroscopist; and 14 benign and 2 malignant ulcers were not seen by the roentgenologist at the first examination (Table 1).

Table I

Summary of 123 cases in which ulcerating lesions were identified by either the gastroscopist or the roentgenologist or by both

Means of Identification	Number of Lesions	
	Benign	Malignant
Gastroscopy and roentgenology	63	20
Roentgenology	22	2
Gastroscopy	14	2

Ulcers Not Seen by the Gastroscopist. Seven of the 22 benign ulcers not seen by the gastroscopist lay in regions designated by the gastroscopists as "blind" areas—namely, the lesser curvature and the adjacent posterior wall of the antrum; a strip of the posterior wall of the body over which the instrument slides; and the extreme upper portion of the lesser curvature. The other 15 were situated on or near the lesser curvature about half way between the gastric angle and the esophageal orifice (Fig. 1). It is not yet clear why the majority of ulcers overlooked by the gastroscopist lie in this region, since the mid-lesser curvature of the body is presumably within the range of the objective of the gastroscope. The lesser curvature as defined by the anatomist and as seen by the gastroscopist is not always the same as that seen by the roent-

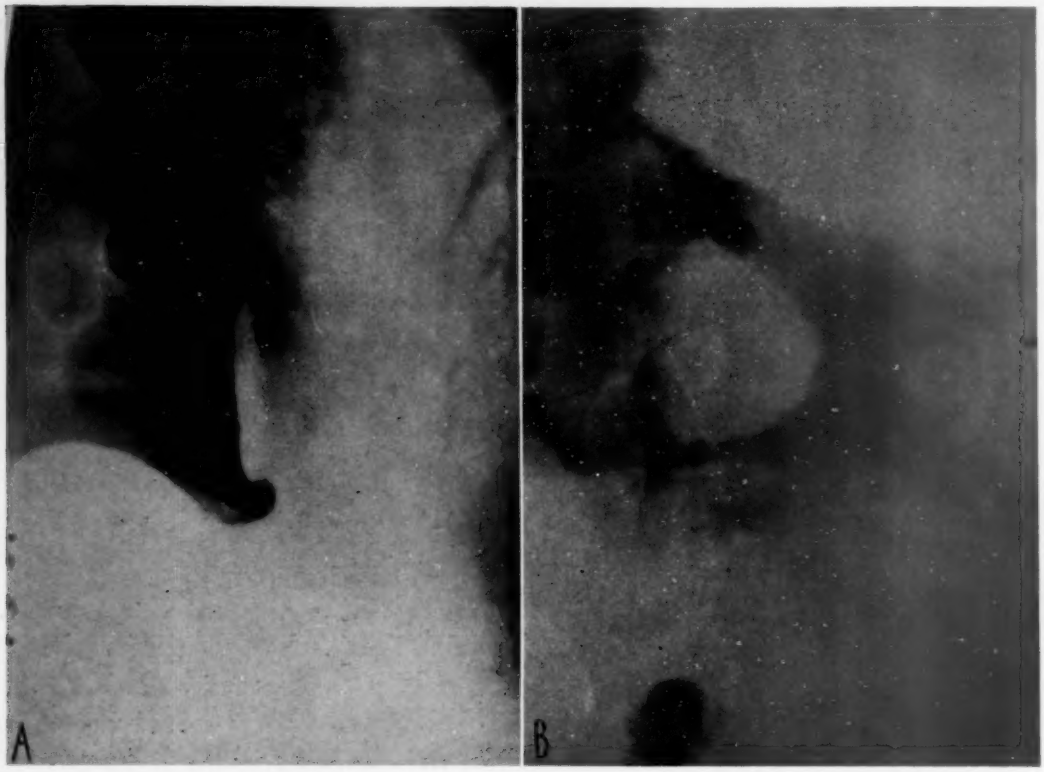

FIG. 1. A large ulcer on the lesser curvature of the stomach seen "en profile" in *A* and "en face" in *B*. Four gastroscopies were performed. The lesion was not seen at the first two attempts. The rolled-up margin was seen at the third attempt. A diagnosis of neoplasm, probably inoperable, was made. At the fourth gastroscopy, done three years later, a diagnosis of benign ulcer was made. At the time these views were made the roentgenologist was unable to differentiate between benign ulcer and ulcerating cancer.

genologist, who is in the habit of considering the medial margin of the stomach as the lesser curvature regardless of the direction of the roentgen beam. Since most of the ulcers reported as lying on the lesser curvature at roentgen examination are brought into profile by having the patient stand or lie in a right anterior oblique position, a great many are probably situated on the posterior wall near the anatomical lesser curvature. If this is true, the blind area of the posterior wall is larger or more medially placed than the gastroscopist realizes or sections of the lesser curvature and adjacent posterior wall cannot always be visualized.

The 2 pathologically proved ulcerating cancers not seen by the gastroscopist but identified by the roentgenologist lay in the blind area of the antrum.

Ulcers Not Seen by the Roentgenologist. Thirteen of the 14 benign ulcers not seen by the roentgenologist were shallow and lay on or near the musculus sphincter antri. The fourteenth, judged deep enough to retain sufficient barium to show at roentgenoscopy or on films, lay high on the posterior wall and bled at the time of gastroscopy. It is postulated that a blood clot prevented barium from entering the crater.

One of the two ulcerating cancers not recognized by the roentgenologist but visualized by the gastroscopist lay high on the posterior wall. The other lay on the lesser curvature above the angle. The first patient had a pronounced cascade stomach, obesity and pernicious anemia with marked spinal cord symptoms. Furthermore, he was examined at a time when the tilting filming-fluoroscope was not available.

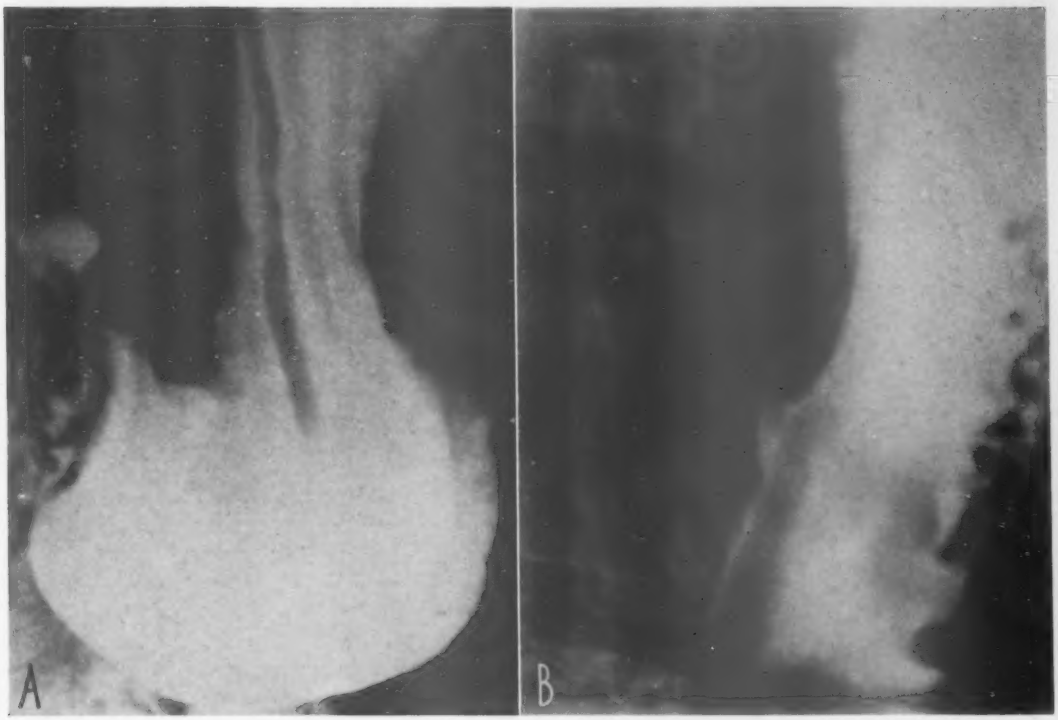

Fig. 2. A shallow ulcer in the middle of a superficial infiltrating carcinoma was found at postmortem examination. At the first examination nothing abnormal was seen at roentgenoscopy but the slight irregularity immediately above the lesser curvature, *A*, warranted re-examination. The second examination produced the same results as the first examination. At the third examination careful application of pressure indicated the presence of radiating folds, *B*. The gastroscopists maintained that a lesion was present at each of three examinations. They definitely diagnosed carcinoma at the third examination.

These difficulties, plus the fact that the patient could not stand, made adequate roentgen examination impossible.

The second patient had a small, flat, ulcerating cancer on the lesser curvature above the angle. The lesion was found at autopsy and the case is reported in detail by Palmer.[12] At the first roentgenoscopic examination nothing abnormal was seen but on the films a small pointed projection on the lesser curvature above the angle suggested a very small neoplasm (Fig. 2*A*). When the roentgenoscopic study was repeated, no abnormality was seen but again the roentgenographic appearance suggested a lesion. During this time the gastroscopist saw a lesion but was unable to make an unqualified differentiation between benign and malignant ulcer. Two months later, after medical treatment, the gastroscopist reported, "Ulcerating carcinoma on the lesser curvature above the angle." At a roentgen examination two days later, compression over the suspected area revealed a shallow, linear ulceration at the hub of radiating folds (Fig. 2*B*). In view of metastatic lesions in bones and the gastroscopic findings, a diagnosis of ulcerating infiltrating cancer was made.

These 2 cases illustrate the difficulties encountered at roentgen examination and the importance of gastroscopy as an aid in visualizing gastric carcinoma. The first case emphasizes a limitation of the roentgen examination. In thick-set or obese individuals with cascade stomach the region high on the posterior wall is difficult to examine. If the region is not adequately visualized in such patients, the roentgenologist recommends gastroscopy. We choose to call this

TABLE II

SUMMARY OF 45 CASES IN WHICH INFILTRATING LESIONS WERE IDENTIFIED BY EITHER THE GASTROSCOPIST OR THE ROENTGENOLOGIST OR BY BOTH*

Means of Identification	Number of Lesions		
	Chronic Gastritis Necessitating Differentiation from Neoplasm	Lymphosarcoma	Carcinoma
Gastroscopy and roentgenology	4	2	25
Roentgenology			5
Gastroscopy	4*		1
	1		
Neither gastroscopy nor roentgenology			1
Gastroscopy and roentgenology. Not confirmed at exploratory laparotomy	1*	*Benign polyp* 1	

* All cases proved by pathologic examination except those marked with *.

region a "roentgenologic blind area" if the lesion lies outside the barium stream as it enters the stomach and if the patient is too obese to allow a clear image on the lateral projection. Unfortunately, in some instances this region is also a blind area at gastroscopy.[19]

The second case illustrates the importance of roentgenograms made under roentgenoscopic control and with compression. The lesion was not seen at roentgenoscopic study by a senior roentgenologist even though he had knowledge of the suspected location at repeated roentgenoscopic examinations.

Infiltrating Lesions

Chronic inflammation and carcinoma are the most common infiltrating diseases of the stomach. With the present methods of roentgenologic diagnosis, chronic gastritis, the most frequent pathologic diagnosis made by the gastroscopist, is only suspected in a very limited number of the cases; and in these cases the possibility of cancer cannot be ruled out with any degree of assurance. As a rule, the diagnosis of infiltrating cancer in the advanced stages gives no trouble to either the gastroscopist or the roentgenologist. In the early stages, before a large section of the stomach is involved or ulceration has occurred, the diagnosis is a rarity. Just why lesions of this type, measuring less than 4 or 5 centimeters in diameter or length, are not found more frequently is not known. Perhaps the explanation lies in the mode of origin. Some workers, attempting to establish an etiologic relation between chronic gastritis and gastric cancer, indicate that the infiltrating cancer is a fusion of many small foci which simultaneously undergo a malignant change.[10]

The difficulties encountered in identifying the infiltrating lesions are illustrated by studying 45 cases in which infiltrating cancer was suspected (Table II). In 4 cases of benign gastritis and 2 cases of lymphosarcoma, the problem was one of differential diagnosis and not visualization of the lesions. No trouble was experienced by either method in identifying the advanced cancerous nature of the other 25. In the remaining 14 of the 45 cases, 5 were not seen by the gastroscopist but were found by the roentgenologist; 6, suspected by the gastroscopist of harboring a cancer, were reported "normal" by the roentgenologist; 1 was not seen by either method; and in 2 a cancer diagnosed by each method was not found at surgical exploration.

Lesions Not Seen by the Gastroscopist. Three of the group of 5 cancers not seen by the gastroscopist but identified by the

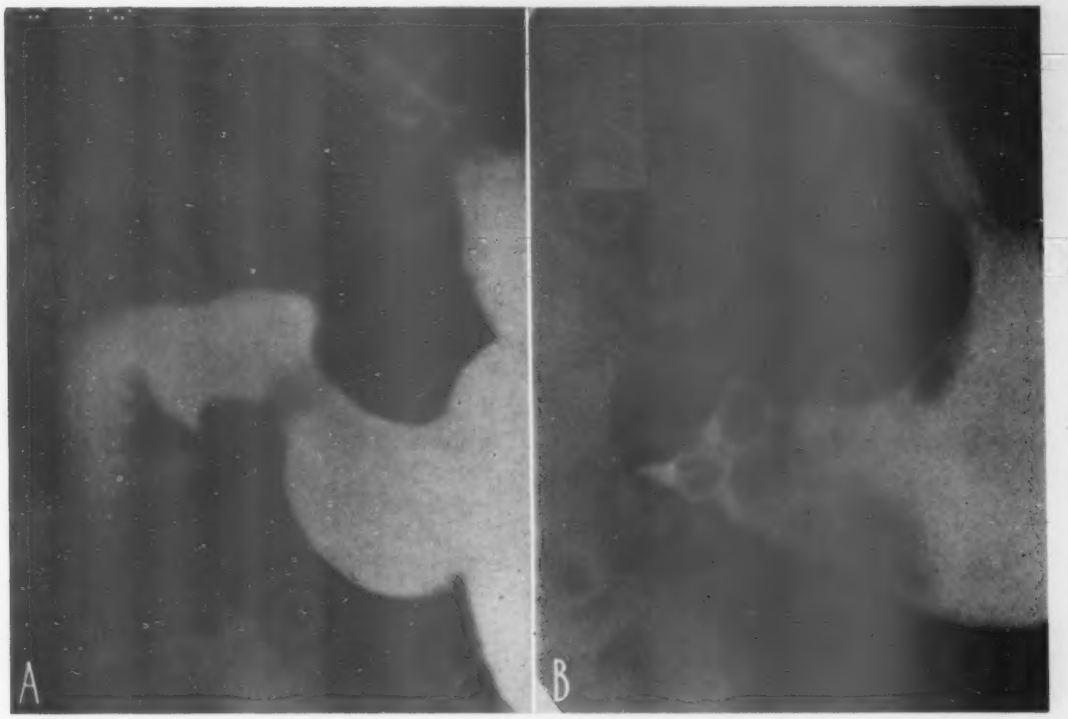

Fig. 3. A small, infiltrating, polypoid carcinoma of the antrum. *A*, filled stomach; *B*, after application of pressure. At gastroscopy the report of the first examination read, "No pyloric tumor visible. Reddening of pyloric ring and obstruction beyond the pyloric ring proved by retroperistalsis and retention of food." At a second examination done ten days later, the report was, "Extremely small nodule on the anterior circumference of the pylorus. It is hard to reconcile the gastroscopic with the x-ray picture." A subtotal gastrectomy revealed three polypoid elevations in an infiltrating cancer that extended down to the pyloric canal.

roentgenologist are members of a relatively large series of cases which cannot be adequately examined with a gastroscope. These 3 cases are included because the gastroscopist attempted to do the examination and they illustrate the difficulties which he encounters. In one an hour-glass deformity of the body and in another stenosis of the lower esophagus prevented the gastroscopist from seeing the neoplasm. The third was a scirrhous carcinoma which had involved the entire stomach. In all 3 cases resistance at the time of introduction of the instrument or regurgitation of air with each puff of the inflating bulb suggested the presence of a pathologic condition. Resistance met at the time of introduction is not sufficient evidence upon which to make a diagnosis of disease, however, for in a number of cases the lesion was not detected at roentgenologic examinations performed both immediately and many months after an unsuccessful attempt to introduce the gastroscope.

In the fourth and fifth cases, contraction ahead of the antral cancer evidently prevented visualization of the lesion at gastroscopy. In the first instance the gastroscopist reported, "Stiff antrum with the angulus region remaining in half spasm throughout prolonged observation so that the involved portion of the antrum remained entirely hidden." At roentgen examination the distal 4 cm. of the antrum was abruptly narrowed and stiff and was associated with a palpable mass. The mucosa in the involved region was replaced with polypoid masses. Biopsy of a gland in the left clavicular region showed metastatic cancer.

In the other case the report of the first gastroscopic examination read, "No tumor visible. Reddening of the pyloric ring and obstruction beyond the pyloric ring proved

by retroperistalsis and retention of food. The visualization of the pyloric canal speaks in favor of a malignant lesion of the pyloric canal but duodenal ulcer cannot be ruled out." At a second examination, done ten days after the first and six days after the last roentgenologic study, the report read, "Today there is no sign of pyloric obstruction. Two extremely small nodules at the anterior circumference of the pylorus are seen. A lesion of the pyloric canal cannot be excluded but it is difficult to reconcile the gastroscopic picture with the roentgen picture." Three roentgenologic examinations were done within a two week period before a final diagnosis of polypoid infiltrating cancer of the distal portion of the antrum was made (Fig. 3). The pathologic specimen obtained by surgical resection contained a papillary tumor with nodules, measuring up to 2 × 2 × 1.5 cm., which encircled the pylorus and extended into the antrum for a distance of 3.5 cm.

These 2 cases and the peculiar contraction of the antrum described by Schindler and Dailey[17] in a case of benign ulcer lend support to the contention of Lintott[11] and Walters[21] that "spasm" can occur in front of a lesion, preventing the gastroscopist from observing the pathologic condition

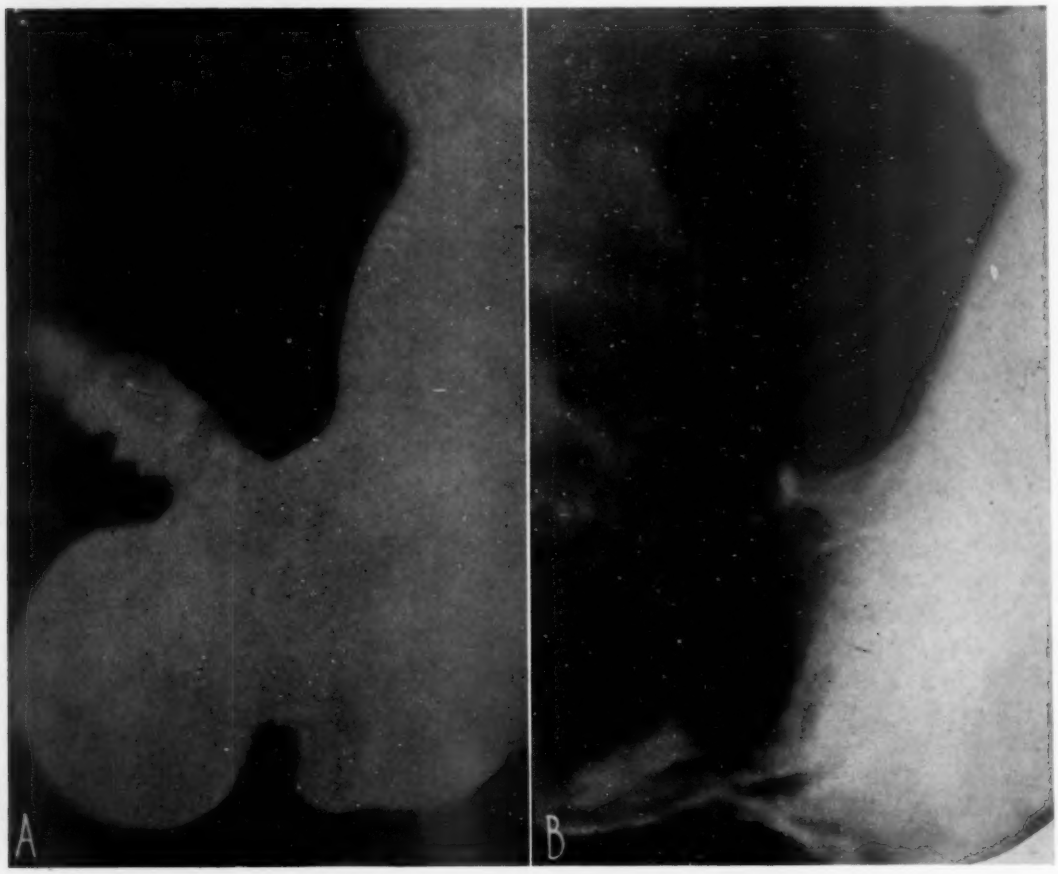

FIG. 4. Ulcer in the pyloric canal. *A*, the uncompressed stomach and *B* the compressed stomach. At postmortem examination a crater was found in the pyloric canal. A long ulcer scar extended up the lesser curvature and shortened it, producing the so-called "rolling up" of the antrum. At gastroscopy two openings were seen, one in the center of the field, which was called pylorus, and one beneath the fold of the gastric angle, which was not definitely identified. It is evident that the lower opening was formed by a contraction of the "pseudo-pocket," formed by the contraction of the lesser curvature and that the upper opening was the true pyloric opening.

(Fig. 4). That a contraction of the central or proximal portion of the antrum might be mistaken for pylorus was suggested by Forssell[7] in 1913, after he had studied the gastroscopic descriptions of Elsner.[5]

Lesions Not Seen by the Roentgenologist. In 6 patients the gastroscopist suspected or diagnosed the existence of an infiltrating cancer not seen by the roentgenologist. In 4 cases, not operated upon, the signs suggesting the possibility of cancer disappeared at subsequent examinations. At the initial examination of these patients the gastroscopist was not able to distinguish definitely between malignant neoplasm and one of the various types of chronic gastritis. It is probably significant that in none of the cases, easy to examine at roentgen examination, was there a suspicion of lesion, even after the results of the gastroscopic examination were known.

One of the 2 cases that underwent pathologic studies proved to be a carcinoma. The roentgenologist noted a persistent narrowing of the distal 4 cm. of the antrum, which was recorded on the roentgenograms. At gastroscopic examination six days later, a tumor-like protrusion was noted along the posterior portion of a large, stiffly infiltrated, ulcerated area above the angle near the lesser curvature. A diagnosis of infiltrating carcinoma was proved by microscopic examination of the specimen obtained by partial gastric resection. The sections of the antrum contained only shallow ulcerations and inflammatory cells. On reviewing the roentgenograms, all made of the stomach distended with barium suspension, a segment of the lesser curvature above the angle was unusually straight, finely serrated and slightly depressed below the remainder of the curvature (Fig. 5). It seems evident that the roentgenologist became so engrossed in the narrowed antrum that he failed to examine adequately the rest of the stomach.

In the other patient the diagnosis is open to debate. A man, aged sixty-three, entered the hospital complaining of epigastric distress of four years' duration, loss of strength, appetite and 30 pounds in weight. The distress was relieved by belching but not by food, milk or alkalies. The gastroscopist reported, "Diffuse, infiltrating, hemorrhagic, ulcerative lesions of large portions of the greater curvature. In addition, there is marked atrophic gastritis of the upper anterior wall. Although all kinds of infiltrating lesions must be considered (chronic hypertrophic gastritis, syphilis, lymphoblastoma, etc.), I believe that an infiltrating type IV carcinoma is most likely. I have never seen such a severe hypertrophic gastritis but I have seen several cases in which such a severe hemorrhagic gastritis hid an infiltrating malignant lesion." The conclusions from a roentgenologic examination made six days later read, "Fluoroscopic examination of the filled stomach showed no evidence of carcinoma but failure of the cardia to balloon out completely and marked irregularity of the upper greater curvature are suggested on mucosal films. Although the mucosal pattern is not typically normal, I would not venture a diagno-

Fig. 5. Cancer of the lesser curvature of the body of the stomach, overlooked by the roentgenologists but found by the gastroscopists.

FIG. 6. At exploration of the stomach, done at the time of a projected cholecystectomy, a small, nonulcerating cancer of the stomach in the region of the gastric angle was found and removed by a subtotal gastrectomy. Although there was distortion of the fold pattern along the lesser curvature in the region of the gastric angle, the roentgenologist was unwilling to diagnose cancer in view of normal roentgenoscopic findings, seen at three separate examinations. The gastroscopists diagnosed hypertrophic gastritis.

sis of lesion in this region were it not for the knowledge of the gastroscopic findings." A second gastroscopy, performed the day after the roentgen examination, and another three weeks later confirmed the original findings. At an exploratory laparotomy done a month after the patient was first seen, the surgeon palpated what he thought to be a normal stomach. Biopsy was taken from the suspected region. Microscopically the mucosa was almost completely atrophic with a tremendous lymphocytic infiltration. Some erosions were seen. The opinions of the pathologists were divided, some diagnosing a lymphoblastoma and others an unusual form of gastritis. The patient received two courses of radiation therapy; one, given a month after surgery, was delivered in eight days and consisted of 1,600 r, measured in air; and a second course, two months later, was delivered in six days and consisted of 1,250 r, measured in air. Three gastroscopic studies, one performed three months after the last course of radiation therapy, failed to show improvement. However, the patient was free of symptoms. The failure of the lesion to improve, as seen gastroscopically, after radiation therapy and the fact that the patient felt well and had developed no signs of lymphoblastoma after a period of two years following the operation are more suggestive of a gastritis than lymphoblastoma.

Lesions Not Found by Either Method. The lesion not definitely diagnosed by either examiner was a soft, infiltrating, submucosal neoplasm which was passed as gastritis by the gastroscopist but found by the surgeon at the time of a projected cholecystectomy. The roentgenologist had refused to make a diagnosis of cancer in the face of suspicious roentgenographic evidence, as no abnormality was seen at three independent roentgenoscopic examinations (Fig. 6).

Lesions Diagnosed by Each Method but Not Found at Surgery. The two stomachs containing the peculiarities diagnosed as neoplasm by both the gastroscopists and the roentgenologists felt normal to the surgeons at laparotomy. As the suspected regions lay high on the posterior wall, biopsy was not attempted. A similar experience is cited by Flexner and Fleishman.[6] In one patient the roentgenologist reported, "Polypoid defect along the medial portion of the dome of the stomach, possibly a polypoid type of infiltrating neoplasm." The gastroscopist recorded, "Tumor of the fornix immediately below the cardia." A differentiation between carcinoma and myoma could not be made but the diagnosis of myoma was favored. At postmortem examination done seven months after the laparotomy, a slightly elevated area, measuring 2 cm. in diameter and located above the cardia,

proved to be a benign polyp at microscopic examination. In the other patient an infiltrating cancer, high on the posterior wall, was favored by both the gastroscopist and the roentgenologist. It is unlikely that this patient had a cancer, for a neoplasm the size of that indicated on the roentgenogram should be easily palpated at laparotomy. The findings were probably caused by some form of gastritis or peculiar arrangement of normal folds. Both of these cases and the one described earlier illustrate the fact that both the roentgenologist and the gastroscopist will occasionally diagnose as neoplasm certain conditions that cannot be palpated by the surgeon, and that the surgeon cannot rely on palpation to rule out the existence of certain types of lesions.

DIFFERENTIATION OF LESIONS

Polypoid Lesions

Roentgenologists and pathologists studying the gross specimen realize that a differentiation between benign and malignant polyp is often little more than a guess. Some gastroscopists do not admit difficulty in making this differentiation. Schindler and Giere[18] write, "In polypoid types of tumors, gastroscopy can show malignant development at its inception." Benedict[2] cites one case of pathologically proved polyp, correctly diagnosed by gastroscopy but called carcinoma by the roentgenologist. Insufficient material does not permit a definite statement but the one case proved by pathologic examination indicates that the gastroscopist as well as the roentgenologist cannot always make this differentiation. The report of the first gastroscopic examination read, "Circumscribed tumor of the upper posterior wall. I believe that this is one of those slowly growing tumors which develops on the soil of an atrophy. However, probably microscopically signs of malignancy could be found. The surface appears too irregular to permit the diagnosis of a benign tumor." Two roentgenologic examinations were conducted, each by a different examiner. One reported, "Large soft mass protruding from the mucosa of the stomach at the lesser curvature of the pars media, presumably medullary carcinoma." The other reported, "Polypoid mass giving the gross appearance of a benign polyp but, of course, the differentiation between a benign and malignant polyp can scarcely be made." After operative excision, evidences of malignancy were not found at pathologic examination.

Ulcerating Lesions

Roentgenologists and pathologists, confining their study to the gross specimen, cannot differentiate between certain types of gastric ulcers and ulcerating cancer. Gastroscopists disagree about their abilities to make this differentiation. Schindler and Giere[18] believe it can be done, for they write, "The differential diagnosis between benign and malignant ulceration is not difficult to determine after a gastroscopic examination by one trained in this field and even in the very early stages biopsy is not necessary." Abel[1] reports that the question cannot be settled by gastroscopy, histopathologic study remaining the only means. Rogers[13] called a benign ulcer malignant.

The following series of cases indicates that the gastroscopist is as prone to make mistakes or express indecision as is the roentgenologist.

Twenty-eight of the 33 cases proved by pathologic examination presented to each examiner the problem of making this differential diagnosis (Table III). In 14 a correct diagnosis was made by both examiners; in 14 an unqualified correct diagnosis was made by the gastroscopist in 7, by the roentgenologist in 3 and by neither in 4. In the 7 cases correctly diagnosed by gastroscopy the roentgenologists were not willing to attempt a final differentiation until after a period of medical treatment. Five of these lesions were benign and 2 were malignant. The 3 correctly diagnosed by the roentgenologist were malignant. In all of these the gastroscopist qualified his diagnosis but gave preference to malignancy. The 4 not definitely diagnosed by either method were all malignant. In all 4 the roentgenologist

did not attempt to make the differential diagnosis. In 3 the gastroscopist could not make the distinction and in 1 the lesion was called benign.

Thirty-five of the 58 cases having benign ulcers, which were proved by complete disappearance of the crater with subsequent normal appearing and pliable mucosa except for small scar, were studied both gastroscopically and roentgenologically. A correct unqualified diagnosis by both examiners was made in 27. In 5 of the 8 remaining cases, cancer was not ruled out by the roentgenologist; and in 2 of the same group the gastroscopist did not rule out this condition until after a period of medical management. The eighth case, called carcinoma by the gastroscopist and not differentiated by the roentgenologist at the first examination, was correctly diagnosed by both after a period of medical management.

TABLE III

SUMMARY OF 28 PATHOLOGICALLY PROVED ULCERS IN WHICH DIFFERENTIATION FROM BENIGN OR MALIGNANT LESION WAS ATTEMPTED BY EITHER THE GASTROSCOPIST OR THE ROENTGENOLOGIST OR BY BOTH AT THE FIRST EXAMINATION

Means of Establishing the Correct Diagnosis	Number of Lesions	
	Benign	Malignant
Gastroscopy and roentgenology	2	12
Gastroscopy	5	2
Roentgenology		3
Neither gastroscopy nor roentgenology		4

Most of the difficulties in differential diagnosis arose because of the morphology of the lesion. In 2, however, the gastroscopist encountered difficulties by attempting to make the differentiation when only part of the lesion was seen (Fig. 1). These were ulcers seen tangentially, in which only portions of the rolled-up margins, which hid the craters, were observed.

Infiltrating Lesions

Schindler's[15] statement that the differentiation between certain types of chronic gastritis and infiltrating cancer is often difficult or impossible to make by gastroscopy holds true for the roentgenologist. In 24 pathologically proved cases having infiltrating lesions, both examiners erred or qualified their diagnoses in the same group of 5 cases, 4 of which were gastritis and 1 carcinoma. In the 4 cases of gastritis, 3 were called carcinoma by each examiner and the fourth was correctly diagnosed by each examiner after a period of management. The carcinoma could not be differentiated from gastritis by either method.

DISCUSSION

Visualization of Lesions

We agree with Berg[3] that the roentgenologic demonstration of a gastric mucosa normal in every respect excludes gastric neoplasm. Unfortunately, however, it is not always possible by roentgen examination alone to explore every square inch of the gastric mucosa, and in some patients the limitations are considerable. Gastroscopy, therefore, is a companion method, desirable and essential in patients whose stomachs cannot be adequately examined roentgenologically.

Two patients in whom cancer was not found by the roentgenologists because of inadequate examination were easily examined by the gastroscopists and cancer was found. In 2 other patients, distorted rugal patterns on films raised the roentgenologist's suspicion of lesion but a definite diagnosis was not made, as nothing abnormal was seen at roentgenoscopy. In 1 the gastroscopists failed and in the other succeeded in confirming the presence of cancer. Likewise, cancer suspected at gastroscopy should be confirmed at roentgenologic examination. In 6 patients the gastroscopists considered the possibility of cancer, not found at adequate roentgenologic examination. In 1 cancer was confirmed and in 1 not confirmed by pathologic studies. In 4 the gastroscopist could not confirm his findings at subsequent examination.

Two patients, in whom both the roentgenologist and gastroscopist diagnosed cancer, submitted to laparotomy. In each instance the stomach felt normal but the mucosa was not inspected nor biopsy made. One patient underwent postmortem examination seven months after the operation and a benign polyp was found. The other patient is still living and, as far as can be determined, does not have a cancer. Insufficient data prevent us from advocating biopsy in cases in which both the roentgenologist and the gastroscopist diagnose cancer not evident to the surgeon by palpation. Whether enough of these cases will prove to have cancer and thus justify the additional surgical risk of biopsy remains to be determined.

Differentiation of Lesions

In the differentiation between polypoid and infiltrating lesions the gastroscopist proved to be no more or less accurate than the roentgenologist. Lesions in which the gastroscopist at the first examination suspected cancer not confirmed by the roentgenologist nor by the gastroscopist at subsequent examinations were explained by the gastroscopist on the basis of a chronic gastritis.

The gastroscopist spoke of cancer in only one ulcerating lesion that was not observed by the roentgenologist. This exception was a patient in whom adequate roentgen examination was not performed. In the ulcerating lesions observed by both methods, the gastroscopist proved to be more accurate in making the differentiation. How much more accurate the gastroscopist is than the roentgenologist cannot be stated from the existing data. The roentgenologist recognizes the cases in which an attempt to make the differentiation is little more than a gamble. As a result, the diagnosis usually read, "Benign ulcer? Ulcerating carcinoma?" without effort to express a preference. By following this technique they escaped completely miscalling the nature of the lesion.

In some instances the roentgenologist was certain of the differentiation when the gastroscopist was not. These included cases giving the meniscus sign[4] in which the gastroscopist saw the lesion tangentially and thus was not able to observe the margins of the crater, an essential to his diagnosis. The gastroscopist exerted every effort to make the differentiation and, as a result, completely miscalled the nature of the lesion in 2 instances. In other patients in whom the gastroscopist was not absolutely certain, a preference was expressed. In most cases the preferential diagnosis was the correct one.*

Gastroscopists are still striving to establish their criteria for differentiation between benign and malignant ulcer. Whether they can improve their ability to make the differentiation or will become more cautious remains to be proved. One thing is certain, a trial by clinical management, as outlined by Palmer,[12] is as applicable to gastroscopy as to roentgenology.

CONCLUSIONS

From the data obtained we believe that the following conclusions can be drawn:

1. In most instances a gastric cancer visible by one method is demonstrable by the other and will be diagnosed correctly by both the gastroscopist and the roentge ologist.

2. Sometimes a lesion, by virtue of its location and morphology, is visible only to the gastroscopist or to the roentgenologist.

3. Occasionally lesions that are demonstrable by both methods are diagnosed malignant by one examiner, benign by the other, and when the facts finally become known it will be found that the gastroscopist is no more or no less likely to be correct than is his colleague, the roentgenologist.

4. A combination of gastroscopy and roentgenology will result in a higher per-

* Those who compare the figures of the correct diagnosis made by the gastroscopists as given in this paper with those listed in papers published by the gastroscopists, drawing on the same material, will find a considerable discrepancy. In this paper diagnoses in which the gastroscopists mentioned both "benign" and "malignant" even though they favored only one were listed as qualified. This qualification was not always considered by the gastroscopists in compiling their figures.

centage of correct diagnoses than will the use of either procedure alone.

REFERENCES

1. ABEL, W. Grenzen der röntgenologischen Magendiagnostik unter besonderer Berücksichtigung der Gastroskopie. *Ztschr. f. ärtztl. Fortbild.*, 1938, *35*, 73–78.
2. BENEDICT, E. B. Gastroscopic observations in neoplasm. *New England J. Med.*, 1936, *214*, 563–566.
3. BERG, H. H. Röntgenuntersuchungen am Innenrelief des Verdauungskanals. Georg Thieme, Leipzig, 1930.
4. CARMAN, R. D. New roentgen-ray sign of ulcerating gastric cancer. *J. Am. M. Ass.*, 1921, *77*, 990.
5. ELSNER, H. Gastroskopie. Georg Thieme, Leipzig, 1911.
6. FLEXNER, J., and FLEISHMAN, A. Analysis of 256 gastroscopies performed at Bellevue Hospital. *Am. J. Digest. Dis.*, 1940, *7*, 323–324.
7. FORSSELL, G. Archive und Atlas der normalen und pathologischen Anatomie in typischen Röntgenbildern. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, Erganzungsband 30, 1913.
8. FREEMAN, E. B. Gastroscopic study compared with other methods of diagnosis in gastric lesions. *J. Am. M. Ass.*, 1939, *112*, 217–222.
9. GRAY, H. K. Carcinoma of the stomach. *J. Am. M. Ass.*, 1941, *116*, 22–25.
10. KONJETZNY, G. E. Der Magenkrebs. F. Enke, Stuttgart, 1938.
11. LINTOTT, G. A. M. Some observations on clinical value of gastroscopy. *Guy's Hosp. Rep.*, 1938, *88*, 422–431.
12. PALMER, W. L. Benign and malignant gastric ulcers; their relation and clinical differentiation. *Ann. Int. Med.*, 1939, *13*, 317–338.
13. ROGERS, H. W. Gastroscopy. *Proc. Roy. Soc. Med.*, 1939, *32*, 519–526.
14. SCHINDLER, R. Gastroscopy: The Endoscopic Study of Gastric Pathology. University of Chicago Press, 1937, p. 301.
15. SCHINDLER, R. Gastritis simulating tumor formation. *Am. J. Digest Dis.*, 1939, *6*, 523–529.
16. SCHINDLER, R. Personal communication.
17. SCHINDLER, R., and DAILEY, M. E. Gastroscopic observations on gastric motility. *Am. J. Digest. Dis.*, 1941, *8*, 8–10.
18. SCHINDLER, R., and GIERE, N. Gastric surgery and gastroscopy. *Arch. Surg.*, 1937, *35*, 712–765.
19. SCHINDLER, R., and HERNANDEZ MORALES, F. Gastroscopic inspection of the pylorus. *Am. J. Digest. Dis.*, 1940, *7*, 242–244.
20. SCHLOSS, J., ETTINGER, A., and PRATT, J. H. Diagnosis of diseases of the stomach by gastroscopy and x-ray relief studies. *Am. J. M. Sc.*, 1937, *193*, 171–180.
21. WALTERS, W. Surgical treatment of ulcerating gastric lesions, with correlated roentgenologic studies. AM. J. ROENTGENOL. & RAD. THERAPY, 1940, *43*, 819–825.

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ROENTGENOGRAPHIC STUDY OF CRANIOFACIAL DYSOSTOSIS*

REPORT OF CASES: NONFAMILIAL AND NONHEREDITARY

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IT IS known and acknowledged by the majority of authors who have studied this subject that the cases of pathological dysostosis of the skull are not all included in the affections described by Comby and Pierrot-Lape[18] under the title of "Nonfamilial and nonhereditary craniofacial dysostosis," nor can we include them all in the syndrome described by Crouzon[17] and emphasized by Regnault and Crouzon,[41] Pesme,[35] and Van Lint[46] under the title of "Hereditary craniofacial dysostosis, Crouzon type" nor can we include them absolutely in the descriptions made by Apert and Bach,[1] Apert,[2] Vaumont,[47] Bianchini,[3] Bertolotti,[4] Schmidt,[41] Coldstream,[16] and others, under the names of oxycephaly, acrocephaly or tower skull. That is to say, that we accept with Isola[28] that these skull pictures are produced by the existence of pathological dysostoses or synostoses in the vault as a result of which anomalous developments of certain regions of the skull are produced, presenting the different forms previously cited and others which we will describe later.

Also as Isola says, isolated synostoses of the vault and face may occur, as he has demonstrated, showing the changes in the roentgenogram of this region. Therefore, we believe that in studying the different cases of craniofacial deformities, associated or solitary, we should make a roentgen study to demonstrate the sutures which are changed and to determine whether the deformities of the skull result from them and also decide from multiple projections whether one, several or all of the sutures are altered.

From this, the theory of Isola[28] seems to be very acceptable to us; it explains the different modifications according to the following statement: "The skull with pathological synostosis of a suture develops very little in the direction perpendicular to the affected suture, while it develops in an exaggerated way in the direction parallel to it." It is clear, as Haas[27] says, that it is difficult in practice to reach an exact conclusion as to whether or not a suture presents complete synostosis.

We shall describe the types of skull pictures resulting from synostosis, following the classification of Isola.

1. The trigonocephalic skull described by Bourneville[7] under the name of oxytrigonocephaly, but more commonly known by that of egg-shaped head, is characterized by a backward flattening of the forehead, which is wide and terminates above in a projection, giving the anterior plane of the face a triangular appearance. There is a compensatory development of the posterior part of the skull, resulting in much greater deformity of the skull. In these cases the metopic or frontal suture is involved in the synostosis; it normally ossifies in the seventh to eighth week. For this reason a roentgen study should be made in the frontal projection. There will be an increase in the horizontal diameter from the great development of the posterior part of the vault and the descent of the base of the skull, resulting from the development of the brain downward because it is prevented from developing forward. These same causes produce a flattening of the sphenoid and ethmoid with consequent decrease in

* Translated from the Spanish by Audrey G. Morgan, M.D.

the development in depth of the orbit.

2. Scaphocephaly, which has been described by Papillault and Desoille.[36] This is characterized by an enormous development of the vault in the anteroposterior direction with a great increase in its diameter with manifest projections in the frontal and occipital regions. On the contrary, the skull is very little developed in the transverse direction, and its transverse diameter may be decreased in comparison with that of the skulls of other individuals of the same age. As may be readily understood, the suture affected is the sagittal or interparietal, which normally completely ossifies quite late; which explains the picture resembling the hull of a boat or an ellipsoid seen in the roentgenogram. In these cases we see, particularly when we use posterior or anterior projections, that the interparietal suture is completely solidified, and in the lateral projection we have been able to show in the 2 cases which we have had occasion to study that in addition to the general roentgen characteristics of all the pathological synostoses of the vault, which we will describe later in a general way, there are zones of hyperostosis, with an undulating and rugose appearance in the upper part of the parietal bone.

Also because of the tendency of the brain to develop downward, there is a prolapse of the base of the skull, most marked in the middle and posterior fossae, as a result of which in the lateral projection we see the image of the base represented by an inclined plane.

3. Platycephaly. This is characterized, as its name indicates, by a skull flattened at the vault, with a depression at the vertex, so that in the lateral projection there is a flat boundary plane instead of a convex one at the highest part of the skull. If we accept the theory of Isola it is easy to understand that the sutures affected are those of the lower part of the circumference of the skull and the frontal pterygoid and mastoid. As a result of this, there is an accentuated development of the occipital fossa with depression and deformity of the base of the skull.

4. Plagiocephaly or asymmetrical skull is characterized, as its name indicates, by asymmetrical development, with an accentuated protrusion of the frontal on one side and of the parietal on the other. There may be anomalies of development in other parts of the skull, but they must always be of an asymmetrical form to constitute plagiocephaly. The sutures affected by synostosis differ in different cases, but we must always look for them following the theory of Isola in a direction parallel to the greatest development of the protrusion, although as that author indicates, secondary manifestations of the synostosis may present themselves characterized by the presence of changes in other sutures which later produce fresh anomalies in the configuration of the skull.

When the same change is shown in the face it is called plagioprosopia and very frequently, as in our case, it happens that plagiocephaly and plagioprosopia are associated.

5. Acrocephaly, described by Apert[2] under the name of acrocephalosyndactylia, has since been discussed by Bertolotti and Boidi-Trotti,[6] Caussade,[13] Nicolás,[34] and others, being confused by many authors with oxycephaly, which we shall describe later, in order that we may see the differential characteristics between these two forms of skull.

Acrocephaly is characterized by a notable reduction in the anteroposterior diameter of the skull with a great increase in the vertical diameter, from the fact that the bregmatic region is situated very high up and is bounded by a plane surface, this being one of the most important characteristics which distinguishes the acrocephalic from the oxycephalic skull.

The acrocephalic skull has been called "tower skull" by Campbell[14] and Schmidt,[41] Mehner,[31] Irion,[29] and Schinz;[42] "policeman's cap" by Comby and Pierrot-Lape,[18] Crouzon,[17] Apert,[2] and "fireman's helmet"

by Bertolotti,[5] this description being accepted by Isola,[28] Castronovo,[15] Guarini,[22] and others.

The sutures which present synostosis in these cases are the highest part of the coronary and the anterior part of the sagittal, as well as the bregmatic fontanelle. As a result of this, there is a very manifest compensatory development in the posterior part of the skull, and a less intense one in the anterior part, the protrusions in the parietal region being quite marked. The protuberances in the frontal region are another characteristic in the differential diagnosis from the oxycephalic skull as they are not seen in the latter. There are also deformities at the base of the skull from prolapse of the latter, which presents the form of an inclined plane; frequently, as a result of depression of the spheno-ethmoidal region, there is a notable decrease in the development and depth of the orbit, with exophthalmos.

6. Oxycephaly may be said to have been described by Mackenzie in 1854 since he called attention to deformities of the skull as a cause of blindness, though he did not distinguish between the different forms of skull. Since then there have been many publications on cranial synostoses which have named them poorly according to our conception, since they only called them oxycephaly, considering them as an entity separate from the other forms of skull which we have described. For instance, Fletcher[21] describes various cases, defining them as an acquired disease characterized by a deformity of the skull in the shape of a tower, with varying degrees of exophthalmos and more or less loss of vision. As Simon, Ramos and Eldridge[44] say, the disease is not necessarily acquired, nor does it necessarily present exophthalmos or loss of vision, as it is much more frequently congenital and also familial. The work of Sharpe,[43] Bronfenbrenner,[8] Bardanzellu,[9] Merlini,[33] Raverdino,[39] Worms and Carillon,[49] and Galstaun[23] emphasize the deformity of the skull following dysostosis of the suture, accompanied by the other two symptoms described.

Oxycephaly is characterized by the head having the shape of the end of a bullet, as Isola says, or a tower shape, according to Fletcher,[21] showing a plane forehead with the bregma situated at the highest point of the skull, so that there is an increase of the vertical diameter of the skull with a decrease of the bitemporal diameter, and the superciliary and temporal borders only slightly marked. It is generally accompanied by the other changes which we will describe later as quite characteristic of all these different forms of skull.

The base of the skull presents a depression at the middle fossa, as a result of which we see in roentgenograms in the lateral projection an abnormal image of the sella turcica characterized by increased breadth and erosion. There is also a less intense prolapse of the spheno-ethmoidal region and quite frequently a decrease in the development of the orbital fossa in the anteroposterior direction, which in many cases, but not in all, is the cause of the exophthalmos which is present.

In these oxycephalic skulls the primary synostosis is in the coronary suture throughout its length, which results in a compensatory development of the posterior part of the skull with prolapse of the base. Greig[24] gives the name of oxycephaly to all the cranial and craniofacial synostoses, since he includes all of them in the classification which he makes. He divides them into the three following groups:

1. True oxycephaly, which is a congenital malformation, manifest at birth and associated with a general synostosis of all the sutures of the skull, producing the typical deformity, and with defects in development such as exostoses of the extremities and syndactylia. In this group he includes acrocephalosyndactylia, as he considers it a true oxycephaly if all the sutures of the skull are ossified prematurely.

2. In this group, called late oxycephaly, he includes all the cases in which the syn-

ostosis begins to develop in early childhood with the oxycephalic skull developing later but with no concomitant defects of the skeleton.

3. He includes in this group the cases which he calls false oxycephaly because they are not congenital and because the synostosis is limited to one or two sutures. We believe that it is better, as we said in the beginning, to call all these cases cranial or craniofacial dysostoses or synostoses, adding to each the distinct form of skull which it presents and which we have described previously, since in addition to the synostosis there are a series of characteristic roentgen signs for all of these skull pictures.

Crouzon[17] distinguishes craniofacial dysostosis from oxycephaly, believing that they are completely distinct manifestations, which he bases on the following differential characteristics: (1) craniofacial dysostosis presents a marked bregmatic protrusion, accompanied by deformity of the face, which is rare in oxycephaly; (2) craniofacial dysostosis is congenital and oxycephaly appears at the age of two or three years; (3) the exophthalmos is more intense in dysostosis than in oxycephaly; (4) dysostosis is hereditary, while this is exceptional in oxycephaly; (5) roentgenographically in both there is an intense cerebriform appearance with some parts of the bone in a laminated form, and with the other roentgen characteristics which we shall describe later, but in oxycephaly there is an intense descent of the middle cranial foss and in dysostosis the latter is oblique.

We believe that none of these differential data between the two affections are absolute, as we have already said that there are cases of craniofacial dysostosis with the acrocephalic form, in which there is a marked protrusion in the bregmatic region, equal to that in oxycephaly, but in the latter it is in a more acute form, the shape of the end of a bullet, while in dysostosis it is more flattened, in the shape of a truncated cone. Moreover, there is no doubt that there are cases of craniofacial dysostosis with skulls of the oxycephalic form, accompanied, as is natural, by deformities of the face; also cases of oxycephalic skull have been described, and we have one, in which the manifestations are evident from birth, which indicates that the synostosis is intrauterine. These cases of oxycephalic skull from craniofacial dysostosis may be accompanied, as in our case, by exophthalmos.

Therefore we are of the opinion, as is Castronovo[15] that in craniofacial dysostosis we should include oxycephaly, general or partial, with skulls of the trigonocephalic, scaphocephalic, plagiocephalic, plagioprosopic and acrocephalic forms, the hypertelorism of Greig, the acrocephalosyndactylia of Apert and perhaps also chondrodystrophia; that is to say, as Bertolotti and Isola state, it is very difficult or almost impossible to differentiate the two affections, and therefore we shall content ourselves from the roentgenographic point of view with making a diagnosis of pathological synostosis with the form of skull that is presented in the different cases, and from the clinical point of view whether it is congenital, familial or hereditary; indeed this dysostosis may be included in Crouzon's disease or Apert's disease according to the case, remembering always that there are cases of true craniofacial dysostosis, or Crouzon's disease with the other symptoms described as accompanying this disease, without their being familial or hereditary. In order better to understand all that we have said, we insist anew on the conception which we hold with respect to all these affections which have been described under different names by different authors.

We believe that there is to be considered a large group which we will call pathological synostoses or dysostoses, as a general rule of the skull and the face, but that as Isola says these may occur separately. When there are synostoses of both regions and in addition they are congenital in character, we include them in the group called by Crouzon craniofacial dysostoses, for which reason some authors have called them Crouzon's disease, and if they are also

accompanied by changes in the extremities, with hyperostosis or exostoses or syndactylia, we shall call them acrocephalosyndactylia.

It may occur as in the first group of the classification of Greig[24] that there are synostoses of all the sutures of the vault of the skull, and then as a result of this there may be the most varied forms according to what was the primary synostosis; for this reason we do not accept, as Greig does, the idea that all the cases of complete synostoses of all the sutures of the skull have the oxycephalic form since, as we have said before, the suture which is affected in the latter is the coronal throughout its length, though it may happen that synostosis of the rest of the sutures occurs secondarily. Therefore we may have cases of the type described by Greig in which, in spite of the fact that there are synostoses of all the sutures at the time the roentgen examination is made, the skull does not show the oxycephalic form, but may be acrocephalic, trigonocephalic, plagiocephalic or scaphocephalic, because the primary synostosis is not in the coronal suture, but in those to which, as we have said before, the different forms of the skull are due.

These varieties of the form of the skull may be found as a result of the different synostoses, and it often happens that for this reason the above-named primary protrusions or tumors may exist corresponding to development following Isola's law, but that in almost all the cases there are other bone protrusions called secondary, as a result of the expansive force of the brain which seeks to expand at the places where there are no synostoses of the sutures.

Therefore in practice we may encounter cases with different clinical and roentgen pictures which are more or less striking, depending on the intensity of the changes. In the first place, we have familial and hereditary craniofacial dysostosis in which, as a general rule, there are synostoses of almost all the sutures of the skull and face, with modifications in the external appearance of the face and the roentgen picture is intensely marked, as we shall see in the detailed description of this affection. In the second place, there is the acrocephalosyndactylia of Apert, also congenital, in which there are the same changes in the skull and the face, but accompanied by exostoses of the extremities and syndactylia of the hands and feet.

In the third place there are the isolated cases of craniofacial dysostosis which are neither hereditary nor familial, which as a general rule present the same clinical and roentgen characteristics as Crouzon's disease.

Finally, there are the facial dysostoses with changes in the external appearance of the face and in the roentgenography of this region without any other symptomatology, and the localized dysostoses of the skull which lead to the different isolated forms of trigonocephalic, platycephalic, plagiocephalic, acrocephalic, oxycephalic or in rare cases microcephalic skull. In some cases, in addition to the cranial dysostosis, there is also a facial dysostosis and then we call it Crouzon's disease, or nonfamilial and nonhereditary craniofacial dysostosis.

The pathogenesis of craniofacial dysostosis has been much discussed, Greig[24] holding that it may be primary or secondary, the latter resulting from traumatism during labor, or rickets, or osteitis of the skull which produce thickening and hyperplasia of the bones and closing of the sutures. The cases described by Castronovo[15] are not conclusive in defense of any of the pathogenic factors cited by many authors. One of the first theories was that of Virchow[48] who, basing his conclusions on the autopsy data obtained in some cases, holds that the synostoses result from bacillary meningitis during fetal life. Although this may be an etiological factor in some cases, we believe that there are a larger number of cases of pathological synostosis which do not show any symptoms of bacillary meningitis. In those which we have been able to study there was no clinical manifestation of this disease; moreover, it is rare for it to be transmitted from parents to children, and

in the familial and hereditary cases it does not explain the facial dysostosis which is sometimes seen isolated and in many cases associated with cranial dysostosis.

According to Isola[28] the different etiologic factors may be included in some of the following groups, although it is accepted by the majority of authors that cases are seen in practice which cannot be included in any of them.

1. The infectious theory of Virchow on which we have already commented.

2. The traumatic theory which may be conceived of as being true because of the greater or lesser degree of trauma suffered by the mother during pregnancy or direct trauma to the head of the fetus on delivery. Although there are some cases which have such a history it must be admitted that in a much larger percentage no such history exists.

3. Specific hereditary diseases, chiefly syphilis, have been given as the cause by some authors. In our cases we were not able to demonstrate such a diagnosis either in parents or children.

4. Isola[28] cites changes in the fetal membranes, but this theory seems to have few advocates.

Finally, the Italian school has defended the endocrine theory of Pende[37] who believes that among the glands of internal secretion the one that is most important in the development of synostoses is the thyroid; he thinks that such synostoses may be produced by a condition of fetal hyperthyroidism which may in some cases be stimulated pathologically by hereditary causes.

Isola gives the following hypothesis: He thinks the predisposing cause is a fetal hormonic disequilibrium (particularly a hyperthyroidism) and, as occasional concomitant causes, infection, trauma, hereditary syphilis, hereditary tuberculosis, amniotic changes, etc.

We have seen in some cases a history of pathological delivery and in the case of the most intense synostosis there was hyperthyroidism in the mother.

Park and Powers[38] believe that synostosis is produced by a defect in the germ plasm.

After having made these comments on etiology, we shall give a brief description of each one of the affections the fundamental anatomical symptom of which is synostosis. First we shall take hereditary craniofacial dysostosis, a disease described by Crouzon[17] in 1912 which is characterized by the triad, deformity of the skull, deformity of the face and ocular disturbances, to which may be added its hereditary and familial character. It is very common in these familial cases to find completely healthy children of parents who have the disease, while other children have an appearance similar to that of the parents with all the characteristics of the disease. The features of the disease are very typical; it shows a very intense exophthalmos, an elongated nose with the shape of a parrot's beak and prognathism of the lower maxillary. The exophthalmos may be accompanied by deviation and decrease or loss of vision. Cases have been described with mental retardation and others with good intellectual faculties.

The changes in the skull are the forms which we have described, such as tower skull, scaphocephalic skull, etc., the most frequent forms in this disease being the oxycephalic and the acrocephalic. The orbits are not very well developed in the anteroposterior direction and are increased in transverse diameter. The appearance of the face is characterized by an increase in the zygomatic diameter, inferior prognathism, nose of the shape of a parrot's beak, high ogival palate and development of the sinuses varying in the different cases, as there are some in which these and the mastoids are not developed, and others in which there is completely normal development. The other changes we shall describe under the roentgen characteristics common to all the cases of synostosis, although as can readily be understood they are more or less intense depending on the severity of the process. We have not been able to study any of these familial cases.

In sporadic craniofacial synostosis, neither familial nor hereditary, the same characteristics are presented as those we have described for Crouzon's disease from which it can be distinguished only by the family and personal history.

The acrocephalosyndactylia of Apert may have the same characteristics and physiognomy of the skull and face as the two affections previously described, but as we have said before, they tend to be accompanied by syndactylia of the hands or feet or both, and by exostoses of the extremities.

The cases described by the name of oxycephaly, such as those of Simon, Ramos and Eldridge,[44] Galstaun,[23] and others, as a general rule have the same clinical and roentgen characteristics, and they are named for the form which the skull takes without indicating the synostosis of the sutures.

Like Brailsford[10] we think, as we have said before, that in addition to these affections (which are included under the name of pathological synostosis) there may be premature synostosis without the syndromes previously described, but with marked changes in the form of the skull, including the different types that we have already described, such as oxycephaly, trigonocephaly, scaphocephaly, acrocephaly, platycephaly and plagiocephaly. This is what we have found in some cases as will be seen from the roentgenograms and histories, in which there was nothing but the deformity of the skull and perhaps slight deformity of the face, but without exophthalmos, prognathism, parrot's beak nose, etc., and no mental disturbance.

We believe that roentgen study is the most important thing in the diagnosis of the disease. As can readily be understood, it is most interesting to determine the condition of the sutures. Haas[27] indicates the difficulty in being certain in the study of the sutures by means of roentgenography recommending that multiple projections be used. This is due to the fact that the image of the sutures is not characterized solely by the saw-tooth appearance, one bone projecting into the other, but it must be remembered that the image differs at different ages of the child; for example, in the first year of life the picture is characterized by a transparent line of varying size with smooth margins which elongates in the direction of the fontanelle even in the cases in which the latter cannot be detected by palpation. In the succeeding years the external table acquires a dentate appearance, while the suture of the internal table has a linear and very undulating form, which it is very difficult to represent in the roentgenogram and which is projected over the site of the internal table. There has been a great deal of discussion as to which part of the skull normally ossifies first, some authors believing that it is the external table, while others, including Haas,[27] believe that the union begins in the diploe, continuing first into the internal table and ending finally in the external table. A knowledge of these data is of great importance because there may be cases in which the suture is open in the external table while in the internal table it is already fused which indicates that there is a synostosis for the development of the skull since that prevents the possibility of extension of the skull in the direction of the suture. Practically we may accept the theory that a suture does not present synostosis when it is represented in the internal table by a line of less density, even though undulating, and in the external table by a dentate appearance in which the interpenetration of the teeth is not complete, or it may be said not to exist, as the tooth-like projections simply lie opposite each other. In studying cases of pathological synostosis it is necessary to consider all the sutures, since we may find a normal picture with dehiscence in some of them while others show a true synostosis; frequently there are partial synostoses while the rest of the suture remains normal. Figure 10 illustrates this; it clearly shows a synostosis of the lower part of the frontoparietal suture with a normal appearance in the middle and upper thirds, as well as in the fontanelle. The same thing

occurs in the parieto-occipital suture, in which there is a picture of slight dehiscences. In this case there is, as in many of those of synostosis, a cerebriform and digitiform appearance much more marked than that accepted today as normal. At the coronary suture the image of the interpenetration of the external table and the sinuous line corresponding to the internal or vitreous table can be clearly seen.

All these facts must be taken into account because, as in the majority of cases of synostosis, there is a cerebriform and digitiform image in the roentgenogram, which as a rule is quite intense, produced probably by an increase of intracranial pressure; it is very easy for a dehiscence of the sutures which do not show synostosis to occur, and as that is the most striking feature to catch the eye, it is probable that if a detailed study of the rest of the sutures is not made the synostosis will pass unperceived, and only a diagnosis of intracranial pressure will be made.

Therefore another of the roentgen characteristics which is of great importance is this picture of the cerebriform appearance as it is called by Bertolotti,[5] Schinz,[42] and others, or the digitiform appearance as it is called by Béclère,[11] and Cushing,[19] which is produced by the wasting away of the internal table because of pressure by the cerebral convolutions. As a general rule, it is accepted that this is a sign of intracranial pressure, but we believe that it may be seen in cases of synostosis even when there is no increased pressure, since what happens is that when the brain grows in a skull which does not grow in the direction where there is synostosis pressure occurs on the vitreous layer, followed by wasting or erosion, which may, in cases in which the internal layer has already disappeared, produce such an intense atrophy of the diploe that it is represented in the roentgenogram by a shadow like that of a loss of substance.

As shown by Figure 7 this intense atrophy is more frequently seen in the bregmatic and frontal or upper parietal regions than in the rest of the skull, where the cerebriform and digitiform appearance is more intense than it is in the skulls of normal children. Moreover, there is a dehiscence of the parietal and occipital sutures, the picture of the other sutures not being seen because of synostosis.

Another of the roentgen characteristics that has great diagnostic value is the rugose appearance with zones of hyperostosis which is generally seen at the vault of the skull, alternating often with the shadows of atrophy which we have described before.

Very often, particularly in cases of synostosis with oxycephalic skull, the prebregmatic region may be thickened, in spite of the fact that the rest of the skull shows the thinning to which we have referred before. Sometimes in following the course of cases we find that the cerebriform or digitiform appearance seen in the previous roentgenograms has disappeared, in spite of the fact that there has been no clinical improvement in the case. This is the same thing that occurs in tumors of the brain with increased intracranial pressure, and is explained according to Thiel[45] by the fact that the erosion produced by the brain is so intense that it involves the internal table throughout its extent, without leaving the projections corresponding to the brain sutures.

We see in the roentgenograms all the forms of skull which we have described above and we will not repeat them here.

Frequently there are changes in the image of the base of the skull, since in the majority of cases it undergoes changes of considerable importance, these depending very much on the form of the skull. In the cases of trigonocephaly, as in Figure 1, we see a flattening of the ethmoid and sphenoid, which come to be located at the same height as the rest of the base, giving an image with a horizontal line which may be called a "plane base." On the other hand, in cases of acrocephalic and oxycephalic skulls there is a descent of the middle fossa with a normal picture of the sella turcica and somewhat less intense flattening of the ethmoido-sphenoidal region. When this lat-

ter region is not flattened the base is represented by a very intensely inclined plane, as in Figure 7, or completely vertical as shown in Figure 9.

Almost all the cases are accompanied by slight development of the orbit in the anteroposterior direction.

The majority of authors admit definite changes in the image of the sella turcica, Bertolotti having called attention to some cases of adiposogenital dystrophy in cranial synostosis. These appear to be purely coincidental, as it cannot be admitted that synostosis is a result of lesions of the hypophysis or that a large and deep sella turcica results from synostosis. In all of the cases that we have studied, particularly in those of oxycephalic, acrocephalic and scaphocephalic skull, we found a sella turcica very much increased in both its diameters with a surface of corresponding size, but without showing any destruction of any of its parts.

It is common, as has been observed by Isola,[28] Castronovo,[15] and others, to see the sphenobasilar suture clearly open, great development of the occipital fossa being also constant, less so in the cases of trigonocephaly.

In the cases we studied the sinuses of the face were only slightly developed or were even entirely lacking.

The mastoids showed little pneumatization. There was only slight development of the orbit in depth, with rather small facial bones, there being a striking contrast between the great development of the skull and the small face. It is very hard to show the optic foramina because of the form of the skull and the arrangement of the base; we observed in one case an enlarged form with thinning of the walls. These changes have been described by other authors, including Castronovo, Pesme, Isola, and others.

We had occasion to observe 8 cases of pathological synostosis of the vault, the majority of which also showed facial synostosis, of which we will give a brief description of the clinical history and roentgen characteristics.

REPORT OF CASES

Case 1. Girl, aged eleven, born at term with normal pregnancy and delivery; no family history; Wassermann reaction negative in parents and child. From the age of two years an exaggerated development of the skull was noted, which contrasted with the smallness of the face,

Fig. 1. Case 1. Girl, aged eleven. The picture is that of a trigonocephalic skull, quite characteristic, with a cerebriform appearance and dehiscence of the parieto-occipital and frontoparietal sutures. There is hyperostosis in the frontal region.

but without any clinical manifestations until a year ago when she began to have intense pain in the head and decreased vision. During the first years of her life she had had whooping-cough, measles and scarlatina, but they left no sequels. At present she shows normal development for her age and does not show any anomalies of the extremities. She has exophthalmos and a great development of the head in the parietal region contrasting with the small face.

The roentgenogram (Fig. 1) shows a trigonocephalic skull with quite a marked cerebriform appearance in all parts and dehiscence of the frontoparietal and parieto-occipital sutures. There is hyperostosis of the frontal bone and in the parieto-occipital region. The base of the skull shows almost a horizontal level which is produced by descent of the spheno-ethmoidal region; the sella turcica may be considered normal as to size and the sphenoidal sinuses are well developed.

The frontal sinus has not developed. There is only slight development of all the bones of the face. A roentgenogram in the posteroanterior projection shows disappearance of the frontal suture from its being completely solidified.

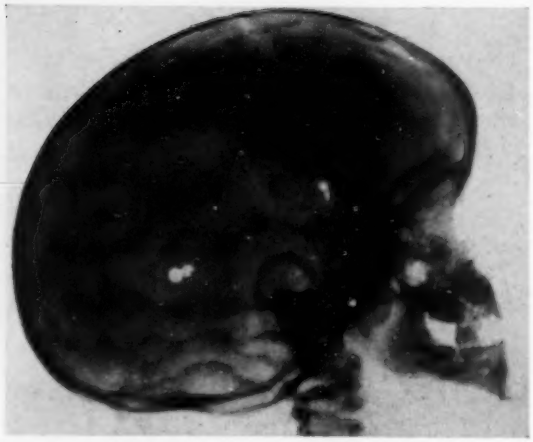

FIG. 2. Case II. Boy, aged five, with abnormal development of the skull from the age of two months. The picture is typical of scaphocephalic skull with very definite increase in the anteroposterior diameter.

CASE II. This is a patient, aged five, in whom the parents noted an anomalous development of the skull from the age of two or three months; they came for consultation because the skull had reached the size and shape shown in the roentgenogram (Fig. 2). There was no family or personal history worthy of mention and the Wassermann reaction was negative in parents and child. Pregnancy and delivery normal.

The image is that of a scaphocephalic skull with definite increase in the anteroposterior diameter because of great development of the frontal and parieto-occipital protuberances. There is dehiscence of the frontoparietal suture, the others being normal. We could not determine the condition of the interparietal suture because we could not get a roentgenogram in the posteroanterior projection but there were some zones of hyperostosis with a rugose appearance at the parietal arch. The cerebriform and digitiform appearance was quite clear, there being thinning of the vault in the frontal and upper parietal regions. The base of the skull had the apperance of an inclined plane, the sella turcica being very much increased in its anteroposterior diameter and there was a large opening in its diaphragm. The frontal and sphenoidal sinuses were not developed in proportion to the child's age. In the face there was only slight development of the maxillary bones with very marked prognathism, the slight development of the face contrasting strongly with that of the skull.

This was a case of craniofacial dysostosis with a scaphocephalic form of the skull, because of localization of the dysostosis in the interparietal suture.

CASE III. The patient was a boy, aged six, who since birth had had a large skull and a small face. The family and personal history were of no importance. Wassermann reaction negative. He was brought for consultation because, in addition to the anomalous development of the skull, there had been intense pain in the head for the past four or five months with decrease of vision. Roentgenograms of the skull in the lateral and posteroanterior projections (Figs. 3 and 4) at first glance seemed to show the picture of hydrocephalic skull, as there was a notable dehiscence of the frontoparietal suture with an increase of the two diameters, particularly the anteroposterior one; but with a little more detailed study we saw a more pronounced cerebriform appearance than normal in the frontal region where the atrophy of bone was so intense that it produced lacunar images. There was also rugosity and hyperostosis in the parietal region and accentuated development of the frontal and occipital protuberances. The base of the skull showed descent, and sella turcica showed an enormous increase of both diameters, more accentuated of the anteroposterior, with decalcification and loss of substance of the anterior and posterior clinoid processes as well as of the quadrilateral

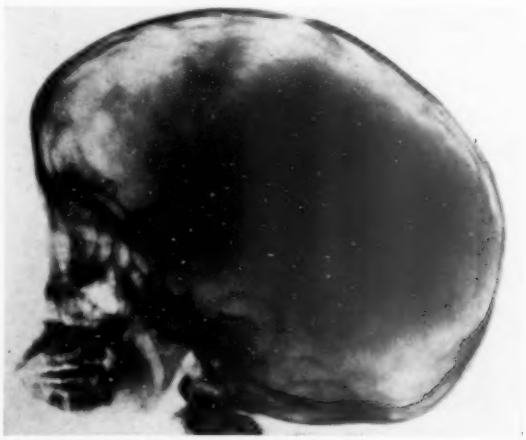

FIG. 3. Case III. Boy, aged six, who from birth showed a large head and a small face. The image corresponds to that of a scaphocephalic skull with plagiocephaly and plagioprosopy as shown in Figure 4.

lamina. There was also a double outline at the bottom of the sella. We believe that this picture of the sella turcica was produced by dilatation of the third ventricle. There was also slight development of the face and decrease in the anteroposterior diameter of the orbit. The maxillary sinuses and ethmoid cells were normal in development. The roentgenogram obtained in the posteroanterior projection is the one that showed the clearest picture of dysostosis, as we saw that the interparietal suture was not represented; it also showed the existence of rugosities in the right external frontal region near the suture, indicating a synostosis of the lower part of the frontoparietal suture which in the roentgenogram showed a normal picture at this site. In this way we can explain the great development with the formation of a pronounced protrusion of the skull on the left side and a less intense one of the face on the same side, constituting the typical picture of scaphocephalic skull, with plagiocephaly and plagioprosopia.

Case iv. Girl, aged seven months, who since birth had had a skull the shape of a boat's hull without any family or personal history worthy of mention. The roentgenogram was made solely for the purpose of studying the picture of the scaphocephalic skull, as the child was brought for examination because of an acute gastrointestinal disturbance, and did not have any clinical manifestations related to the form of the skull. In spite of the fact that we did not obtain an anteroposterior roentgenogram and that in this lateral view the bregmatic region is lacking, we present this roentgenogram (Fig. 5) because it is very typical of the undulating appearance with rugosities and hyperostosis in the parietal region, and also shows the majority of the characteristics described above.

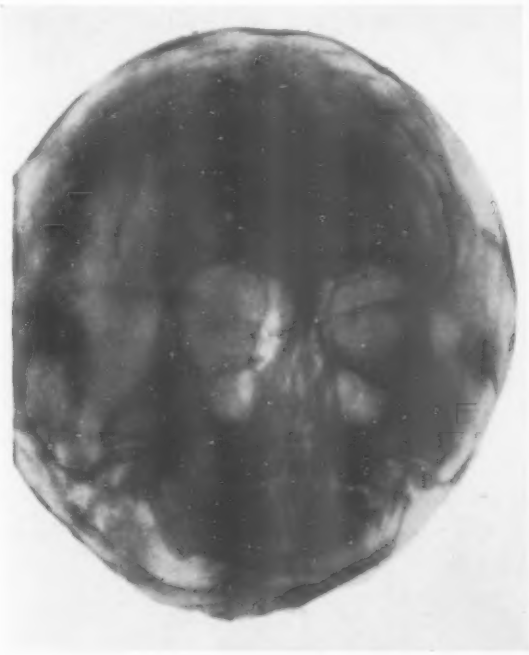

Fig. 4. Case iii. Posteroanterior roentgenogram shows asymmetry of the two sides of the skull and synostosis of the interparietal suture.

Fig. 5. Case iv. Girl, aged seven months. The appearance is that of a scaphocephalic skull with an undulating appearance and rugosities with hyperostosis in the parietal region.

Case v. Boy, aged twelve, with a special form of the skull which does not belong exactly to any of those described above, but is a combination of several of them, as we see a marked increase of the anteroposterior diameter and great development of the occipitoparietal protuberance and the upper bregmatic region, but with a plane boundary. This latter characteristic would cause it to be included in the group of acrocephalic skulls, but in these there is not the increase of the anteroposterior diameter with great development of the posterior part of the vault, but on the contrary there should be a decrease in this diameter. The coronary suture shows synostosis and probably the middle and posterior parts of the intercoronal, the rest of the sutures being normal. To this is due the image in the roentgenogram (Fig. 6) which is that of a skull of the mixed acrocephalic and scaphocephalic forms.

FIG. 6. Case v. Boy, aged eleven. Roentgenogram shows a skull with a mixed acrocephalic and scaphocephalic form.

CASE VI. This patient was a boy, aged nine, with the typical clinical picture of sporadic Crouzon's disease, but there was no family history of a similar appearance of the skull and face. There was one curious fact in the family history, that of the mother having suffered from hyperthyroidism with a basal metabolism of plus 40 per cent, indicating that she already had the symptoms of this disease before pregnancy, which supports Pende's theory discussed above. The Wassermann reaction was negative in parents and child.

From birth the upper part of the skull was seen to be very prominent, with a moderate exophthalmos and slight development of the face which showed a nose elongated in the form of a parrot's beak and prognathism of the superior maxillary. All these symptoms had become exaggerated during the past two years and had been accompanied by pain in the head and decreased vision.

The lateral roentgenogram (Fig. 7) shows a typical image of oxycephalic skull with the bregma situated high up and failure of the coronary suture and bregma to appear, showing synostosis at this site. There is a cerebriform or digitiform appearance of the whole skull which is very accentuated in the upper part of the vault, where the vitreous table is not shown, which produces an image almost lacunar in type at this site. This very characteristic hammered appearance and the rugosities of the vault at some sites with pronounced thinning in others may be considered pathognomonic. In the middle part of the frontal at its anterior boundary there is also a circumscribed zone of thinning. The parieto-occipital sutures show a marked dehiscence. As a result of the marked prominence of the bregmatic part, there is an increase of the vertical diameter, which contributes also to the descent or lordosis of the base of the skull. The anteroposterior diameter of the sella turcica is somewhat increased.

The face is not very well developed in comparison with the rest of the skull.

The previous course showed a stationary stage of the symptomatology.

CASE VII. This patient was a girl, aged four, who since birth had shown this form of skull, typically oxycephalic, slight development of the face and marked exophthalmos. The family and personal history were unimportant. Wassermann reaction negative in parents and child.

All of her progenitors and brothers and sisters were completely normal in physiognomy. As the photographs (Fig. 8) show there is a marked increase in the distance between the eyes with manifest exophthalmos but without prognathism of the lower maxillary. There is increase in the zygomatic diameter and flattening of the interocular part of the nose. The frontal and parietal protuberances are very marked, as can be seen in the roentgenogram.

Development of intelligence normal. She does not complain of pain in the head or have

FIG. 7. Case VI. Boy, aged nine, with a clinical picture of sporadic Crouzon's disease. The roentgen findings are typical of oxycephalic skull with the bregma very high, and synostosis of the coronary suture and of the bregma, with an image almost of the lacunar type around it.

Fig. 8. Photographs of Case VII.

convulsions or loss of vision. There is no Graefe's sign, in spite of the pronounced exophthalmos.

Figures 9 and 10 show all the characteristics described for craniofacial synostosis with oxycephalic skull in a tower shape, showing two very pronounced protrusions, one in the most posterior part of the parietal bone and the other in the prebregmatic region.

In all these zones, or more properly speaking, in all the vault of the skull, there is one of the most typical of pictures, a more than cerebriform or digitiform appearance in the form of a sponge or, as we call it a beehive, produced by the enormous wasting or erosion of the vitreous table and diploe, accompanied, as we indicated in the description of a general nature, by zones of hyperostosis in the internal table, which is what forms these bands and partititons which cross the zones of lesser density, constituting true beehives in the posterior parietal region.

Fig. 9. Case VII. Girl, aged four, who from birth presented this form of oxycephalic skull with slight development of the face and marked exophthalmos. This is one of the most characteristic roentgenographic images in the form of a sponge or as we say a beehive, produced by the tremendous wasting of the vitreous table and diploe, accompanied by zones of hyperostosis in the internal table, which is what forms these bands or partitions which cross the zones of lesser density.

FIG. 10. Case VII. Posteroanterior roentgenogram for better demonstration of the appearance of the orbits and the form of the skull.

Various dense lines of hyperostosis can be seen which cross the skull from the sphenoid to the parietal region; in the occipital, which is not very well developed, there is marked hyperostosis near the fontanelle. There is no image of sutures except in the occipital region, because there is synostosis of all the others. The descent of the base of the skull is very pronounced in the middle and posterior fossae, which makes the anterior part appear completely vertical. The sella turcica, as in all the cases we have studied, is very much increased in both diameters with its diaphragm very open; the sphenobasilar suture is very clearly shown. The maxillary sinuses show normal development. The orbits have almost no development in the anteroposterior diameter and there is little development of the face, particularly in comparison with that of the skull.

The roentgenogram of the optic foramina which we took showed an oval and somewhat reduced image. In these roentgenograms we can appreciate the extent of the zones of hyperostosis, as well as the impossibility of showing the suture because of synostosis in spite of taking roentgenograms in many projections.

We believe that this was a case of sporadic craniofacial dysostosis with a tower-shaped skull.

SUMMARY

As can be seen from the study of these cases and what has been stated above, we believe that in practice we may find subjects who present pathological synostosis of the vault of the skull or of the vault and the face, accompanied as a result of it by different forms of skull, but without presenting the clinical and roentgen picture of craniofacial dysostosis or Crouzon's disease, which is often manifested only by the scaphocephalic, plagiocephalic, and so forth, skull without any of the other clinical manifestations which we have described as characteristic of this disease.

Nor have we seen any cases of tower skull or oxycephalic skull which were associated with hemolytic icterus, as Günther indicates.

We must take into account all the roentgen characteristics, which we have described, in order to make a diagnosis of dysostosis, but as we indicated above, what is most important is the careful and detailed study of the sutures; as we have seen in the majority of the cases a dehiscence of the normal sutures is apparent on the first impression as a result of increased pressure; but if we study one or several projections of the sutures which we suspect of showing

FIG. 11. Case VIII. Illustrative of a synostosis of the lower part of the fronto-parietal suture and a normal appearance in the middle and upper thirds and in the fontanelle, indicating the possibility of the existence of partial synostosis.

synostosis, following the theory of Isola, to which we attribute extraordinary value, we shall see that they cannot be represented roentgenographically since the linear or dentate image considered normal has disappeared because of the pathological synostosis.

REFERENCES

1. Apert, E., and Bach, E. Oxicéphalie. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1928, *52*, 970–975.
2. Apert, E. De l'acrocéphalosyndactylie. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1906, *23*, 1310–1330.
3. Bianchini, A. Su di un caso di acrocefalosindattilia. *Radiol. med.*, 1927, *14*, 1–12.
4. Bertolotti, M. Le syndrome radiologique de l'oxycéphalie et des états similaires d'hypertension cérébrale. *Presse méd.*, 1910, *18*, 946–951.
5. Bertolotti. Trattato di Radiologia. Second edition. Part 1ª, p. 122. Taddei Ferrara.
6. Bertolotti, M., and Boidi-trotti, G. L'acrocefalo-sindattilia di Apert, varietà fetale della craniosinostosis patologica. *Riforma med.*, 1915.
7. Bourneville. Oxitrigonocéphalie atrofie des nerfs optiques. *Compt. rend. de bicètre*, 1895.
8. Bronfenbrenner, A. N. Oxycephaly as a pathogenetic entity. *Am. J. Dis. Child.*, 1931, *42*, 837–857.
9. Bardanzellu, T. Contributo clinico allo studio dell'oxicefalia. *Arch. di oftal.*, 1932, *39*, 201–240.
10. Brailsford. The Radiology of Bones and Joints. Second edition. William Wood & Co., Baltimore.
11. Béclère, A. Le radiodiagnostique et la radiothérapie des tumeurs de l'encéphale. *Rev. neurol.*, 1928, *1*, 885–948.
12. Bernard, P., and Trotot, R. Sur un cas de maladie de Crouzon. Présentation de radiographies du crâne. *Bull et mém. de radiol. méd. de France*, 1936, *24*, 132–133.
13. Caussade, L., and Nicolás. Contribution à l'étude de l'acrocéphalosyndactylie. *Paris méd.*, 1929, *2*, 399–402.
14. Campbell, D. Ueber die Dysostosis cranio-facialis (Crouzon) und die Akrozephalie (Apert). *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1931, *43*, 358–362.
15. Castronovo, E. Sulla craniostenosi familiaire ereditaria. (Disostosi craniofacciale.) *Radiol. med.*, 1931, *18*, 325–346.
16. Coldstream, W. J. A. Case of oxycephaly. *Edinburgh M. J.*, 1927, *34*, 357–363.
17. Crouzon, O. Une nouvelle famille atteinte de dysostose cranio-faciale héréditaire. *Ann. de méd.*, 1929, *25*, 84–91.
18. Comby and Pierrot-Lape. Dysostose craniofaciale non héréditaire et non familiale. *Presse méd.*, 1926, *34*, 947.
19. Cushing, Harvey. Intracranial Tumours. Charles C Thomas, Springfield, Ill., 1932.
20. de Diego, P. Acrocefalo-sindactilia con ectrodactilia y pies varos. *Pediatría espan.*, 1935, *24*, 181–200.
21. Fletcher, H. M. On oxycephaly. *Quart. J. Med.*, 1910–1911, *4*, 385–398.
22. Guarini, C. Considerazioni su tre casi di oxicefalia. *Radiol. med.*, 1924, *11*, 580–585.
23. Galstaun, G. A case of oxycephaly. *Brit. J. Radiol.*, 1930, *3*, 454–455.
24. Greig, D. M. Oxycephaly. *Edinburgh M. J.*, 1926, *33*, 189–218; 280–302; 357–376.
25. Günther, H. Der Turmschädel als Konstitutionsanomalie und als klinisches Symptom. *Ergebn. d. inn. Med. u. Kinderh.*, 1931, *40*, 40–135.
26. Gunsett, A., Sichel, D., and Bouton. Un cas de maladie de Crouzon. *Bull. et mém. Soc. de radiol. méd. de France*, 1933, *21*, 695–697.
27. Haas, L. Ueber die klinische Verwertbarkeit der röntgenologischen Nahtdiagnose. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1930, *41*, 549–571.
28. Isola, A. Le sinostosi patologiche della volta e del cranio facciale. *Radiol. med.*, 1932, *19*, 1382–1438.
29. Irion, O. Ueber die Aetiologie des Turmschädels. *Zentralbl. f. Gynäk.*, 1931, *55*, 207–213.
30. Lape. Cited by other authors.
31. Mehner, A. Beiträge zur den Augenveränderungen bei der Schädeldeformität des sog. Turmschädels mit besonderer Berücksichtigung des Röntgenbildes. *Klin. Monatsbl. f. Augenh.*, 1921, *67*, 204–217.
32. Mackenzie. Cited by Simon, Ramos and Eldridge, ref. 44.
33. Merlini, A. Sulla sindrome di craniosinostosi patologica con speciale riguardo alla oxicefalia. *Chir. d. org. di movimento*, 1923, *7*, 451–517.
34. Nicolás. Contribution à l'étude de l'acrocéphalosyndactilie. Thèse de Nancy, 1929.
35. Pesme, P. Etude radiologique de un cas de maladie de Crouzon. *Bull. et mém. Soc. de radiol. méd. de France*, 1930, *18*, 149.
36. Papillault, G., and Desoille, H. Présentation d'un cas de scaphocephalie. Nosographie des dysostoses craniennes. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1929, *53*, 708–717.
37. Pende, Nicola. Trattato sintetico di patologie e clinica medica. Messina, 1929.
38. Park, E. A., and Powers, G. F. Acrocephaly and scaphocephaly with symmetrically distributed malformations of extremities; study of so-called "acrocephalosyndactylism." *Am. J. Dis. Child.*, 1920, *20*, 235.

39. RAVERDINO, E. Oxicefalia et lesioni oculari. *Arch. di oftal.*, 1924, *31*, 12.
40. REGNAULT, F., and CROUZON, O. Etude sur la dysostose cranio-faciale héréditaire. *Ann. d'anat. path.*, 1929, *6*, 577–594.
41. SCHMIDT, H. Ueber Turmschädelbildung infolge prämaturer Nahtsynostose. Ein Fall beobachtet an Mutter und Kind. *Deutsche Ztschr. f. Chir.*, 1930, *224*, 331–339.
42. SCHINZ. Roentgendiagnostico. Tomo II. Salvat Editories, Barcelona, 1932.
43. SHARPE, W. Cranial deformity of oxycephaly; its operative treatment. *Am. J. M. Sc.*, 1916, *151*, 840–862.
44. SIMON, A., RAMOS, R., and ELDRIDGE, W. W. Oxycephaly; report of two cases. AM. J. ROENTGENOL. & RAD. THERAPY, 1935, *33*, 516–521.
45. THIEL, R. Röntgendiagnostik des Schädels bei Erkrankungen des Auges und seiner Nachbarorgane. J. Springer, Berlin, 1932.
46. VAN LINT. Dysostose cranio-faciale héréditaire, type Crouzon. *Bull. Soc. belge d'opht.*, 1929, No. 59, 28–30.
47. VAUMONT. Cited by other authors.
48. VIRCHOW. Cited by Isola, ref. 28.
49. WORMS, G., and CARILLON, R. Contribution à l'étude de l'oxicéphalie. (Données radiographiques. Troubles oculaires et auriculaires.) *Rev. d'oto-neuro-opht.*, 1930, *8*, 736.

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RIB-LIKE SHADOWS IN THE GLUTEAL MUSCLES PRODUCED BY AN OIL SUSPENSION OF BISMUTH USED IN ANTISYPHILITIC THERAPY*

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WHEN pelvic roentgenograms are made of patients who have received intragluteal injections of an oil suspension of bismuth salts, the bismuth usually appears as large droplets (Fig. 1). Less commonly the shadows may be fan-like, indicating that the oil has diffused along the sheaths of the gluteal muscles (Fig. 2).

In a case recently seen by us, the distribution was of this second type but the bands or stripes were so dense as to suggest that they represented not merely bismuth diffused along muscle sheaths but also calcifying myositis occurring as a reaction to the presence of the bismuth. The opaque bands were so long and dense as to resemble ribs and at first the technician thought that

FIG. 1. Bilateral bismuth deposits in gluteal muscles after several injections.

she had accidentally used for the roentgenogram of the pelvis a film already used for the chest (Fig. 3).

CASE REPORT

R. H., a white male, aged forty, was referred for roentgenograms of the sacroiliac joints because of low backache. His previous history was unimportant except for the fact that during the past ten years he had received numerous bismuth injections to both hips for the treatment of syphilis. His general physical condition was

FIG. 2. Distribution of oil suspension of bismuth along muscular septa and sheaths of gluteal muscles.

good, and his low back pain was usually present after horseback riding, which he indulged in frequently. Roentgenograms (Figs. 3 and 4) made on the patient's first visit revealed rib-like shadows extending from the sacrum into the gluteal muscles which were very distinctly seen in the lateral view. There were four parallel bands of radiopaque material on the left and four similar ones on the right side of the sacrum. Surrounding the outer portions of the bands there were bismuth deposits in droplet form which were best seen in the lateral view. Subsequent roentgen examination of the heart and great vessels showed normal findings. Roentgenograms made three months later (Fig. 5) revealed that the rib-like shadows were of lessened density, which means, of course, that there had been some absorption of the bismuth deposits in the interim. The patient has since become lost to us so that further follow-up films are not available.

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FIG. 3. Spectacular appearance of large amounts of bismuth deposits in gluteal muscles suggesting ribs.

Since an oil suspension of bismuth salts represents a foreign body in the gluteal tissue, it undoubtedly acts as an irritant and is walled up by connective tissue and histiocytes and is transported in the lymph channels. It has been stated by Chizzola[1] that the band-like appearance of bismuth deposits is not exclusively caused by the retention and distribution of bismuth salts, and that a certain amount of shadow is probably due to the parenchymatous or interstitial myositis which leads to degenerative processes of the muscle and deposition of calcium salts. The arguments presented by Chizzola in favor of this theory are: (1) that the intensity of the roentgen shadows is not in proportion to the amount of bismuth injected; (2) the relative rarity of such pictures in syphilitics who have been given bismuth, indicating that in certain individuals there may be special local reactive processes; (3) the similarity of these findings to calcifying myositis; (4) the fact that it has been demonstrated that bismuth injections may cause a myositis.

FIG. 4. Lateral view of same patient as in Figure 3, showing that the bismuth is actually deposited in the gluteal muscles.

FIG. 5. Roentgenogram of same patient as seen in Figure 3 three months later. A large amount of bismuth has been absorbed.

Schreus[2] has observed that the roentgen visibility of bismuth deposits may last for a period of as long as two years depending, of course, on the solubility of the bismuth salt injected. His controlled examinations two and a half, three, and four years after bismuth injections reveal no evidence of a bismuth shadow.

SUMMARY

A spectacular case of rib-like shadows in the gluteal muscles produced by numerous injections of an oil suspension of bismuth

used in antisyphilitic therapy has been presented. It is possible that the distribution of the bismuth deposits in such instances might be more pronounced as a result of muscular activities which bring the gluteal muscles into action. In the case reported, the patient was accustomed to riding horseback three to four times a week, and this may have some bearing on the distribution of the bismuth deposits.

REFERENCES

1. Chizzola, G. Significance of roentgen pictures following intramuscular injections of bismuth compounds. *Radiol. med.*, 1930, *17*, 150–158. Abs. in Am. J. Roentgenol. & Rad. Therapy, 1931, *25*, 144.
2. Schreus, H. Th. On the distribution of bismuth deposits in intramuscular injection of insoluble salts and the duration of their roentgen visibility. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1929, *40*, 42–46. Abs. in Am. J. Roentgenol. & Rad. Therapy, 1930, *23*, 123.

BRONCHOCOLIC FISTULA*

REPORT OF A CASE

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SEVERAL publications in the recent literature demonstrate the value of roentgen examination as a material aid in the diagnosis of internal fistulae. Of these, the bronchocolic fistulae seem to be extremely rare. A search of the literature disclosed only one case, reported by Felkl and Michalek. A brief summary of their case may therefore not be amiss.

A boy, aged six, developed, following a lobar pneumonia, cirrhosis of the left lower lobe and multiple bronchiectases. After scarlet fever, exacerbation occurred, complicated by an encapsulated empyema at the left base. Six days later pulmonary symptoms subsided, and peritoneal symptoms developed in the left epigastrium, as result of perforation of the empyema through the diaphragm into the subphrenium. Ten days later the subphrenic abscess emptied into the eroded colon. Feces contained free pus; the abdominal pain subsided. Sputum examination revealed presence of *Bacillus coli*.

The authors believed that the bronchocolic fistula resulted from an ascending infection from the colon, and was not due to simultaneous perforation into a bronchus and through the diaphragm. If the former were true, at least partial evacuation of the pus through the bronchus would have occurred. The fistula was demonstrated after injection of lipiodol into the left bronchus. On roentgenoscopic examination and also on films a sinus tract could be demonstrated, through which lipiodol emptied partly into the splenic flexure of the colon. Subsequently the patient showed progressive improvement, gain of weight and decreased expectoration.

We have had an opportunity to demonstrate a bronchocolic fistula, which developed as a complication of acute appendicitis. Our observations made on roentgen examination of this case are given in this paper.

H. R., white female, aged sixteen, was admitted to Crippled Children's Hospital in July, 1937. Four days prior to admission, the patient was seized with cramping pain in the epigastrium, followed by vomiting, chills and fever. The next day, the pain was localized in the right lower quadrant. The temperature on admission was 103.2° F. The white blood count showed a neutrophile leucocytosis with many young leukocytes. On physical examination the tongue was dry, the abdomen moderately distended, rigid, diffusely tender and tympanitic on percussion. There was rebound and referred pain; subdued peristalsis was audible over the left abdomen. No peristalsis could be elicited on the right side. A tentative diagnosis of appendicitis and perforative peritonitis was made. The general condition of the patient precluded an immediate surgical intervention, and conservative treatment was instituted. Fluids were given subcutaneously and intravenously; on several occasions blood transfusions were also administered.

Several days after admission to the hospital, the patient complained of pain in the chest, particularly on the right side. There was no cough or expectoration.

A roentgenogram of the chest showed elevation of both diaphragms; both costophrenic angles were obliterated. There was a mottling at the right base. These findings were interpreted as evidence of a subphrenic abscess with sympathetic pleurisy and localized pulmonary atelectasis.

Under conservative treatment patient showed sufficient improvement to permit an operation. The abdominal tenderness became localized to the left lower quadrant, where a mass could be palpated. Under local infiltration, a $1\frac{1}{2}$ inch gridiron incision was made on the left. A large abscess was encountered in the left hypogastrium, containing approximately a quart of thin, flaky, foul smelling pus. The abscess cavity was evacuated by suction and drains were inserted. With adequate drainage from the abscess cavity the peritoneal and septic symptoms subsided.

In October, 1937, there was a recrudescence. The patient complained of severe epigastric pain, particularly in the left hypochondrium.

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The abdomen became distended, there was a tympanitic note to percussion over the epigastrium. These symptoms subsided after several days; the wound closed without an external fistula. The patient seemed to recover satisfactorily.

In December, 1937, the patient was seized with severe pain in the chest, cough, and expectorated moderate amounts of foul sputum. The temperature again assumed a septic character. On physical examination râles were found at the left base.

Another roentgenogram of the chest failed to reveal any evidence of pulmonary lesions. A barium enema was given. The colon showed a good filling with exception of the cecum, which could not be satisfactorily visualized because of considerable pain. During the examination, the patient was suddenly seized with severe cough and expectorated a fairly large amount of barium. The bronchial tree of both lungs was well outlined by the barium solution; there was no evidence of bronchiectasis. In the abdomen a sinus tract could be demonstrated leading from the distal transverse colon toward the left hypochondrium, where a large collection of barium was noted underneath the diaphragm, near the spleen. No communication between the colon and stomach could be demonstrated.

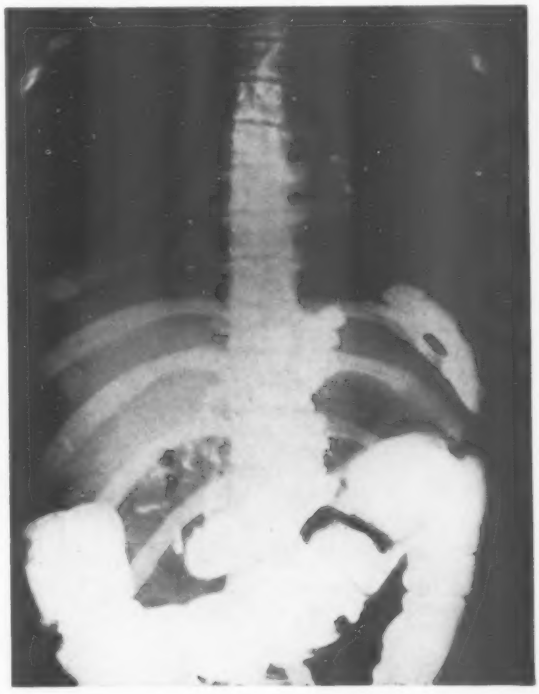

Fig. 1. Barium enema: Fistulous tract extending from the splenic flexure of the colon into the left subphrenium. Large collection of barium underneath the left diaphragm.

Fig. 2. Barium filling the bronchial tree, demonstrating the communication between the colon and the bronchus.

For several weeks, the patient continued to cough and expectorated copious amounts of foul smelling sputum. The treatment was confined to conservative measures.

In May, 1938, an appendectomy was advised. A 2½ inch McBurney incision was made. Very dense scar tissue involving the peritoneum and the transversalis muscle were encountered; while attempting to break through the dense scar tissue of the transversalis, fecal material was noticed. The cecum was found to be involved in the mass of scar tissue. It was then thought best to refrain from the contemplated appendectomy and to insert a drain into the abdominal cavity as a precautionary measure. Four weeks after the second operation, the patient was discharged from the hospital and remained under observation in the out-patient department.

After a short period of relative improvement, she returned to the hospital complaining again of pain in the left lower chest, cough, which grew progressively worse, and was associated with copious amount of foul sputum. The temperature ranged between 100 and 104° F. A roentgenogram of the chest showed a small pleural effusion at the left base. Underneath the left diaphragm there was a fairly large, apparently encapsulated collection of barium from the previous examination. The right lung and diaphragm were normal. Obviously the bronchocolic fistula led to an encapsulated empyema of the left pleural cavity.

In spite of the fact that the patient's symptoms were due to the bronchocolic fistula, a surgical intervention was not deemed advisable. Of necessity, the treatment was confined to supportive conservative measures, and directed primarily toward the pulmonary and pleural manifestations.

COMMENT

From this rather long history it is fairly obvious that following an acute appendicitis and perforative peritonitis, the patient had several intra-abdominal abscesses. Two of them (in the left and right hypogastrium) were drained surgically, and this was followed each time by improvement of the physical condition of the patient.

One abscess was evidently localized underneath the left diaphragm, and was not noticed at the time of the operation. This subphrenic abscess was well encapsulated within peritoneal adhesions into which the splenic flexure of the transverse colon was also incorporated.

As the pressure within the abscess increased, and no external drainage was established, it perforated into a bronchus through the diaphragm and also into the colon. The pus within the subphrenic abscess was evacuated partly through the bronchus and partly into the colon. The foul sputum, expectorated in large quantity, led to the clinical diagnosis of a pulmonary abscess, which could not be substantiated roentgenologically. The not intended bronchogram of the chest failed to demonstrate bronchiectases, which could also account for the pulmonary symptons. When the barium enema demonstrated the bronchocolic fistula conclusively, a chronic ascending infection of the bronchi, caused by the *Bacillus coli*, explained satisfactorily the origin of the expectorated pus and foul sputum.

The remissions of the pulmonary symptoms, followed by periods of new exacerbation, are significant. It seems logical to assume that these remissions were due to temporary closure of the fistula. The fistula could and possibly did seal off either within the wall of the colon, or within the diaphragm. A temporary block within the communicating bronchus was also possible. When pus within the subphrenic abscess reaccumulated and the pressure increased, the fistulous tract was usually re-established, and clinically this gave rise to recurrent symptoms of a pulmonary abscess.

The abscess was again drained through the bronchus and most likely into the colon. At the time barium enema was done, the barium filled the abscess cavity and could be demonstrated on subsequent examinations. The communication of this cavity with the colon facilitated the permeation of colon bacilli and sustaining of an infectious process of the bronchi and also the pleura.

The empyema which later developed must have been encapsulated; this seems to be evident from the fact that it was confined to the base, and was not associated with signs of an acute septicemia, so characteristic of pleural effusion with *Bacillus coli* as the pathogenic organism.

As far as the mechanism of bronchocolic fistulae is concerned, their origin may show certain variations. In the case of Felkl and Michalek, the patient had bronchiectases, and an encapsulated empyema. The empyema ruptured into the subphrenium and later emptied into the colon. The bronchial fistula developed later. The authors assumed that the ascending infection from the colon may have been the causative factor in producing this fistula.

In our case, a subphrenic abscess following an acute appendicitis and perforative peritonitis apparently ruptured simultaneously into the bronchus and colon. The continuous ascending infection from the colon was most likely responsible for the prolonged course of the disease, during which the patient developed a chronic pneumonitis at the left base and an encapsulated empyema.

Bronchocolic fistulae may be produced by direct perforation of an abscess (empyema, or subphrenic abscess). However, Beye feels that some empyemata complicating a subphrenic abscess are due to lymphatic extension of the infection rather

than to perforation of the diaphragm.

The course which the pus follows after perforation of the diaphragm depends evidently on whether or not a free pleural space exists. If the basal pleura is not adherent, perforation is followed by an extensive empyema, which may later rupture into the bronchus. In the presence of adhesions, however, the abscess will rupture into the bronchus, or a small, encapsulated empyema may be formed, which in turn will rupture into the bronchus.

The length of time between the evident onset of symptoms produced by the original focus of infection and the establishment of a bronchocolic fistula is difficult to determine without the study of a larger series of cases.

Ochsner and Graves found that the incidence of all pulmonary complications of a subphrenic abscess rises with delayed diagnosis and treatment. The frequency of this complication depends to a large extent upon the length of time between the formation of the abscess and the time these patients seek medical consultation.

The clinical diagnosis of a bronchocolic fistula may offer great difficulties. This complication should be considered whenever in the course of an empyema or subphrenic abscess the patient develops a sudden, severe pain, cough, and expectorates moderate or copious amounts of foul sputum, without clinical or roentgenological evidence of a definite pulmonary abscess. The examination of the sputum may demonstrate the presence of *Bacillus coli*, and frank pus may be found in the feces.

A roentgenological demonstration of the fistula should be attempted. Bronchography may prove an adequate procedure if the lipiodol should visualize the fistulous tract and empty into the colon. If this method fails to confirm the clinical diagnosis of a bronchocolic fistula, a barium enema should be given. These fistulae may be of a valve type, and it is difficult to predict which of these methods may prove more successful.

CONCLUSION

1. Thoracic or subphrenic suppurations may become complicated by formation of bronchocolic fistulae.

2. The clinical diagnosis of bronchocolic fistula is discussed.

3. This diagnosis is established definitely by roentgenologic demonstration of communication between the bronchial tree and colon.

4. Bronchography and barium enema are considered to represent the necessary procedures in establishing this diagnosis.

REFERENCES

1. Beye, H. L. Thoracic complications of subdiaphragmatic infection. *J. Thoracic Surg.*, 1932, *1*, 655–662.

2. Felkl, H., and Michalek, E. Bronchocolonfistel bei einem fünfdreiviertel Jahre alten Knaben. *Wien. klin. Wchnschr.*, 1936, *49*, 875–877.

3. Ochsner, A., and Graves, A. M. Subphrenic abscess. *Ann. Surg.*, 1933, *98*, 961–990.

INTERNAL BILIARY FISTULA*

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INTERNAL biliary fistulae may connect any portion of the biliary tract with any portion of the gastrointestinal tract, but certain structures appear to be much more frequently involved than others. Bernhard[2] found, in 6,263 biliary operations, 109 internal biliary fistulae: the duodenum was the communicating portion of the gastrointestinal tract in 56 cases; the colon was involved in 36, and the stomach in 12. In 5 of the cases collected by Bernhard, the fistulous connections involved more than one gastrointestinal structure.

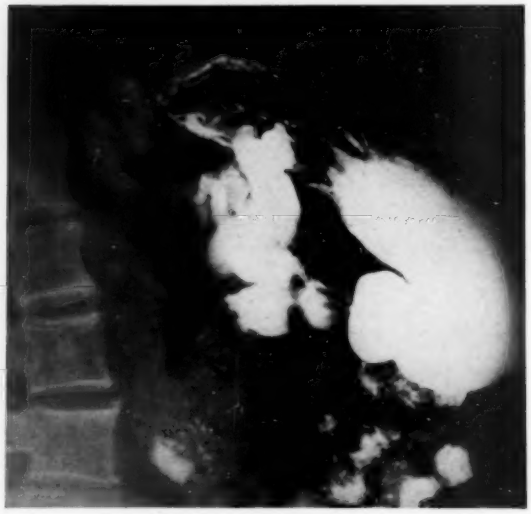

FIG. 1. Case 1. The large irregular shadow proceeding upward from the duodenal cap would appear to represent the common bile duct. Note the air-filled bile ducts (arrows).

Judd and Burden[8] found that in 153 cases the biliary fistula opened into the duodenum in 117, into the colon in 26, into the stomach in 6 and into the duodenum and colon both in 4.

Courvoisier[4] reported fistulae between gallbladder and duodenum in 25 cases, between gallbladder and ileum in 1, and between gallbladder, duodenum and colon in 2.

Gråberger[7] has reported an internal biliary fistula involving a duodenal diverticulum.

In considering the etiology, three factors appear to be of importance. The most frequent of these is the passage of a biliary concrement from the gallbladder or common duct into the duodenum or stomach. More rarely the fistula is formed as a result of duodenal ulcer having caused periduodenal infection and adhesions; still more rarely is cancer the causative factor.

CASE 1. On August 1, 1940, a patient F. M., female, aged fifty-eight, was referred for gastrointestinal examination. The history was that of gallbladder attacks for ten years; she had also been on diabetic regimen for ten years. Jaundice had been present on numerous occasions. At the time of admission there was some rigidity and tenderness in the right upper quadrant.

The blood pressure was 142/74. The urinalysis was as follows: color, amber; specific gravity, 1.032; albumin, trace; glucose reduction with 2 drops of urine; microscopic, few hyaline casts and pus cells.

Stool: four plus blood.

Blood: leukocytes, 14,500; red blood cells, 4,700,000; hb, 90 per cent; color index, 0.95 per cent; differential: neutrophils, 64 per cent; non-segmented, 4 per cent; lymphocytes, large, 18 per cent, small, 10 per cent; eosinophils, 2 per cent; basophils, 2 per cent; nonprotein nitrogen, 17.5, and at two succeeding examinations 43 and 74. Blood sugar (daily): 151, 192, 172, 126.

Upon beginning the roentgenoscopy of the stomach, after two visualizations of the duodenal cap there appeared above the cap a long, irregular shadow. It extended upward to partially overlie the fundus of the stomach. Because of the history of repeated gallbladder attacks, this shadow, after some observation, was taken to be the common bile duct.

With the additional detail available in roent-

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genograms, this impression was confirmed; also there were noted tubular gas shadows in relation to the liver density suggestive of air in bile ducts (Fig. 1).

The five hour film yielded a rather striking visualization of the biliary tree (Fig. 2).

Operation was proposed, but the patient, a severe diabetic, refused.

Our first thought at noting the ready passage of gastric contents into the liver was that such a communication must lead, within a very short time, to marked damage of the liver by infection. It would appear, from some observations which have appeared in the literature, that this does not occur so readily as might seem probable at first consideration. Williams and Smithwick[15] report that the biliary system may function quite normally for many years after the establishment of such a fistula. They discuss the treatment of biliary fistula by implantation into the duodenum, and do not consider that the risk of ascending infection is sufficient to constitute any serious objection to the procedure. They call attention to one case in which the patient's course was uneventful for fifteen years after the performance of such an operation.

Fuller[6] has given details of a case in which, where the fistula connected the colon with the gallbladder, there appeared to be no evidence of liver infection.

On the other hand, Rivers and Mason,[13] who found an incidence of internal biliary fistula amounting to 0.8 per cent in a series of 1,117 biliary operations, consider that these fistulae produce, in time, a considerable amount of chronic hepatitis, and that such patients are poor operative risks. Bernhard[2] gives the operative mortality, in cases of internal biliary fistula, as 10 per cent, though he states that such a fistula is not incompatible with long life, and cites cases in which such patients have lived uneventfully for fifteen and nineteen years.

Fistulae in which barium passes to the biliary tree as freely as in our own case probably consist, for the most part, of those in which the communication involves the common bile duct directly. In a series of 10,866 autopsies Roth found 43 such fistulae. This list was compiled in 1929, and at that time Öhnell and Lindblom[12] record that at the Mayo Clinic only one case had been reported in which there had been a visualization of the bile ducts following barium meal. The literature also contained reports, the same authors go on to state, of a total of only 8 such visualizations at that time.

Fig. 2. Case 1. Note the striking visualization of the biliary tree. Film made five hours after ingestion of the barium.

Visualization of the biliary tree does not always mean that a fistula is present.[1] The contrast meal may pass through the ampulla of Vater in cases in which this structure is patulous and incompetent. Åkerlund has described a case of pancreatitis in which the barium entered both the common bile duct and the pancreatic duct.

Figure 3 represents a case in which, in interpreting the roentgenograms in a gastrointestinal examination, the structure marked by an arrow was described as a duodenal diverticulum. Other circular barium shadows bordering the upper portion of the small bowel likewise seemed typical of di-

FIG. 3. Case II. This structure, reported as a "duodenal diverticulum," was proved at operation to be the fundus of the gallbladder, joined to the descending portion of the duodenum by a fistulous tract.

verticula; the report was accepted by the attending surgeon without question.

The patient, however, had symptoms referable chiefly to the gallbladder, and after repeated attacks was prepared for operation.

CASE II. The patient was a male, E. F., aged sixty-eight. For two years he had had pain in the right upper quadrant of the abdomen radiating to the back. Some of the attacks had been accompanied by chills and fever. His findings at the time of admission to the hospital were as follows:

Urine: specific gravity, 1.018; albumin, trace; sugar reduction with 6 drops; few red blood cells microscopically; few pus cells.

Stool: essentially negative.

Blood: leukocytes, 11,000; red blood cells, 4,240,000; hb, 80 per cent; color index, 0.95 per cent. Differential: neutrophils, 71 per cent; lymphocytes, 21 per cent; eosinophils, 2 per cent; basophils, 0; monocytes, 6 per cent.

Blood chemistry: urea nitrogen, 32; urea, 69; uric acid 3.2; sugar, 118. Chlorides 509; icterus index 42. Kahn reaction, negative.

Basal metabolic rate, plus 10 per cent.

The patient was deeply jaundiced; pulse was 54; respirations, 20; there was marked tenderness and rigidity in the right upper quadrant of the abdomen.

The preoperative diagnosis was chronic cholecystitis and chronic cholangitis, with obstructive jaundice and the possibility of a common duct stone.

The operative findings are quoted as follows (Dr. E. A. Christofferson):

"There were multiple adhesions between the gallbladder and duodenum. There was a fistulous tract between the gallbladder and duodenum. Below this tract the gallbladder was very narrow but free bile was present.

"The gallbladder was separated from its adhesions. The fistulous tract between the gallbladder and duodenum was exposed. The gallbladder was opened and the fistulous tract outlined. The common duct was opened, emptied of its contents, probed, and a tube inserted. A rubber tube was sutured into the fundus of the gallbladder, and the fundus of the gallbladder attached to the anterior parietal peritoneum.

"The common duct was plugged by stones and thick mud from the branches of the hepatic duct to the ampulla of Vater. After emptying the common duct of this material by milking it upward, with scoops, and by irrigation, the common duct was found to be probably occluded by stricture near the ampulla—at least it could not be ascertained definitely to be patent either by probe, irrigation or by examination with finger. Therefore, the fistulous tract between the gallbladder and duodenum was left intact.

"The abdomen was explored and inflammatory masses were found elsewhere in the abdomen. The liver was fairly normal in appearance, somewhat mottled and distended.

"Closure was with one tube in the common duct."

Thus, it was established at operation that the structure marked by the arrow in Figure 3, and which I had described in my report as a "duodenal diverticulum" was in reality the fundus of the gallbladder, joined to the pars descendens of the duodenum by a fistulous tract.

It will be noted that in this case none of the barium had passed upward, and that none of the bile ducts are visualized. This is in accord with our observation above that such free visualizations of the biliary

tree usually occur when the common duct is directly involved by the fistula.

SUMMARY AND CONCLUSIONS

1. Internal biliary fistulae involve most frequently the gallbladder, less frequently the common bile duct; and the gastrointestinal portion of the fistula involves most frequently the duodenum, then the colon, after that the stomach, and very occasionally the duodenum and colon together.

2. The etiologic factors are, in order of their frequency: perforation of a biliary calculus; periduodenal inflammation consequent upon duodenal ulcer; and least frequently of all, cancer.

3. The passage of duodenal contents into the bile ducts is not incompatible with long life, some cases having been observed for fifteen years and more; though chronic infection is engendered, and the operative mortality in such cases is probably almost 10 per cent.

4. Passage of duodenal contents into the liver occurs for the most part in cases in which the fistula directly involves the common bile duct; in fistulae involving the gallbladder this upward passage of duodenal contents occurs much less frequently.

REFERENCES

1. Arntzen, L. Penetration of contrast meal substance from the duodenum into the bile passages via the ductus choledochus. *Acta radiol.*, 1932, *13*, 202–205.
2. Bernhard. Quoted by McQueeney, ref. 10.
3. Butureanu, W., Barth, C., and Gatoschi, G. Ulcère duodénal perforé dans les voies biliaires extrahépatiques (fistule cholédodo-duodénale). *Presse méd.*, 1936, *44*, 2109–2110.
4. Courvoisier. Quoted by McQueeney, ref. 10.
5. Davison, M., and Aries, L. J. Spontaneous choledochogastrostomy and cholecystogastrostomy. *Ann. Surg.*, 1938, *107*, 229–237.
6. Fuller, C. J. Cholecysto-colic fistula with unusual radiographic findings. *Brit. M. J.*, 1930, *1*, 279–280.
7. Gråberger, G. Nachtrag zu dem Aufsatz "Beitrag zur Röntgendiagnose innerer Gallenfisteln." *Acta radiol.*, 1931, *12*, 310–312.
8. Judd and Burden. Quoted by Arntzen, ref. 1.
9. Köhler, B. Du passage du contenu intestinal dans les voies biliaires après papillotomie transduodénale. *Acta chir. Scandinav.*, 1935, *77*, 155–162.
10. McQueeney, A. M. Internal biliary fistulae and intestinal obstructions due to gallstones. *Ann. Surg.*, 1939, *110*, 50–54.
11. Mardersteig, K. Darstellung einer Gallengang-Duodenalfistel bei der röntgenologischen Magenuntersuchung. *Deutsche med. Wchnschr.*, 1932, *58*, 1288–1289.
12. Öhnell, H., and Lindblom, K. Air-filled bile-ducts in a case of fistula between duodenum and common bile-duct. *Acta radiol.*, 1929, *10*, 121–126.
13. Rivers, A. B., and Mason, J. B. Cholecystoduodenal fistula. *Med. Clin. North America*, 1932, *15*, 1571–1579.
14. Swalm, W. A., and Manges, W. F. Visualization of hepatic ducts and common duct with choledochus stasis. *Am. J. Surg.*, 1929, *7*, 521–525.
15. Williams, H., and Smithwick, R. H. Treatment of biliary fistula by direct implantation of the tract into first portion of the duodenum. *Ann. Surg.*, 1929, *89*, 942–945.

DIFFERENTIATION BETWEEN THE DIRECT AND INDIRECT EFFECTS OF ROENTGEN RAYS UPON THE ORGANS OF NORMAL AND ADRENALECTOMIZED RATS*

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IT IS now generally agreed that the primary effect of roentgen rays on living tissues is one of destruction at the point of impact. The possibility of secondary toxic effects after a localized irradiation has also been duly emphasized.[2,6,8,21] However, there exist many conflicting data on the extent and localization of these secondary disturbances. Their importance was so great for some authors that, on the basis of experiments by Schwarz[17] and Werner,[22] they questioned the existence of a direct effect of the rays.[9] On the other hand, Jolly and Ferroux,[9] demonstrating the importance of the local action of roentgen rays, went so far as to attribute even the lesions in the lymph nodes located out of the irradiated field to the existence of scattered rays. These contradictions were apparently due to the absence of a clear line of demarcation between the lesions specifically due to the direct impact of the rays and those which were caused by secondary disturbances extending out of the irradiated area.

In this investigation, the separation of specific and nonspecific effect of the roentgen rays was attempted by examination of the organs located out of a narrow field of irradiation. Thus the thymus was examined when the abdomen was treated; the gastrointestinal tract when the head was irradiated, and so on. In addition, because of the rôle of the adrenals in the response of the organism to toxic agents, all the experiments were duplicated in adrenalectomized animals.

In a preliminary report[19] evidence was produced that irradiation of the abdomen had an effect on organs located out of the irradiated field. However, as this could be peculiar to abdominal irradiations, our observations were continued and extended to irradiation of another region of the body, i.e. the head and neck.

EXPERIMENTAL PROCEDURE

Normal adult, Wistar rats, weighing approximately 150 grams, were irradiated while lying flat on the back. In order to avoid the diffusion of roentgen rays out of the treated zone, the following precautions were taken: (1) the head, abdomen, limbs, and tail of the animals were fixed on a board; (2) a lead plate, 5 mm. thick, covered the whole animal, except for a hole of the desired size cut over the zone to be irradiated; (3) the edges of the hole were slightly bent downward, pressure being exerted on the plate so that the edges of the hole were applied firmly on the skin of the animals, slightly depressing the surface.

In preliminary experiments on direct irradiation of the thymus, a zone 2.5 by 2.5 cm., measured from the anterior tip of the sternum backward, was selected on the middle line. The abdominal irradiation was performed on a surface of 3 cm. long by 5 cm. wide in the lower region of the abdomen. When the neck and head were irradiated, the lead plate covered the body as far as the base of the neck, just above the anterior tip of the sternum.

The conditions of irradiation were as follows: 150,000 volts; 5 ma.; filtration, 1 mm. of aluminum; distance anticathode-skin, 25 to 40 cm.; "casel" constant potential; duration of irradiation, fifteen to sixty minutes. Fairly high doses of roentgen rays were given, except in the case of local irradiation of the thymus (Table 1). At the time when autopsy was performed, namely, forty-eight hours after irradiation (several cases at twenty-four and sixty-six hours), the animals appeared in rather good health.

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However, when the animals were not sacrificed, death occurred spontaneously after six to eighteen days.

The adrenalectomized animals had been operated upon from two to five days before the irradiation. They appeared quite sick at the time of autopsy (forty-eight hours after irradiation) and some died shortly before that time. At autopsy, careful inspection of the suprarenal region was performed to make certain of the absence of adrenal accessories.

The organs of the autopsied animals were weighed and sectioned for histological study. Only the organs showing significant variations were reported in the table.

The results were obtained in two series of experiments. The first series, using male rats, was the object of the preliminary report.[19] The second series, using female rats, produced similar results. Therefore the results were collected in one table.

TABLE I

EFFECT OF A LOCAL IRRADIATION ON DISTANT ORGANS IN PRESENCE OR ABSENCE OF THE ADRENALS

Group No.	No. of Animals	Zone Irradiated	Dose	Adrenal	Thymus	Spleen	Stomach
1	12	Control	None	31 mg.	190 mg.	701 mg.	Normal
2	6	Control	None	Removed	208 mg.	731 mg.	Normal
3	6	Thymus	630 r	28 mg.	48 mg.	710 mg.	Congestion
4	4	Thymus	630 r	Removed	57 mg.	645 mg.	Some ulcers
5	10	Lower abdomen	1980–3680 r	40 mg.	57 mg.	409 mg.	Some ulcers
6	9	Lower abdomen	1980–3680 r	Removed	150 mg.	624 mg.	Ulcers
7	6	Head and neck	2800 r	38 mg.	(45 mg.)	452 mg.	Some ulcers
8	4	Head and neck	2800 r	Removed	(103 mg.)	659 mg.	Ulcers

RESULTS

As a preliminary control, irradiations restricted to the thymic region were performed in normal and adrenalectomized animals (Table 1, groups 3 and 4). In both cases, there was an atrophy of the thymus, which, histologically, could be explained by a widespread destruction of thymocytes in the medullary and cortical regions of the thymic lobule (Fig. 4), as described by Cremieu[1] and by Regaud and Cremieu.[14] With the small dose of roentgen rays used, no effects were observed in other organs with the exception of a slight action on the stomach. Obviously, the tremendous lesions in the thymus were due to the direct action of the rays. Furthermore the sensitivity of the tissue to roentgen radiation destruction was in no way modified by the presence or absence of the adrenals.

When a larger dose of roentgen radiation was applied to the lower abdomen of normal animals (group 5), the *thymus* became atrophied, its weight being reduced to an average of 57 mg. instead of 190 mg. as in the controls. There was a pyknotic destruction of the cells in the cortex of the thymic lobules so that the lobules were greatly reduced in size and the cortices were no longer visible (Fig. 3), resembling the changes reported in various cases of accidental involution.[7] Adrenalectomized animals receiving the same dose of roentgen rays (group 6) did not have an atrophic thymus, theirs appearing normal histologically (Fig. 2) and weighing only slightly less than the controls.[11] The behavior of the thymus after an intense abdominal irradiation was therefore entirely different in normal and adrenalectomized animals. This difference clearly eliminated the effects of scattered roentgen rays in the production of the thymus atrophy in non-adrenalectomized rats after abdominal treatment.

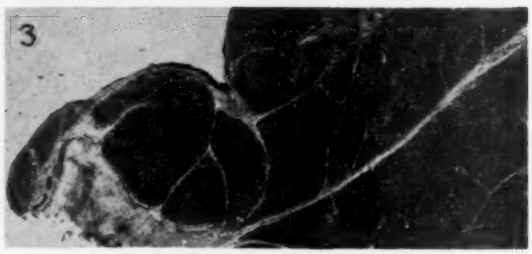

FIG. 1. Normal thymus.

FIG. 2. Thymus of an adrenalectomized animal, having received 2,800 r on the abdomen. Thymic lobules are distinct.

FIG. 3. Thymus of a normal animal, having received 2,800 r on the abdomen. The darker cortex of the lobules has disappeared, through destruction of the thymocytes and constriction of the reticulum.

FIG. 4. Effects of a direct thymic irradiation.

Therefore, irradiation carefully restricted to the abdomen had produced lesions in the thymus as a secondary indirect effect.

In the *lymph nodes* both a direct and indirect effect could also be found. The direct effect observed after abdominal irradiation in the lower mesenteric lymph nodes produced more widespread necroses; the indirect effect was only noticeable in the center of the germinative nodules (mediastinal lymph nodes). It was also observed on histological slides both in the thymus and lymph nodes that the direct effect was fully developed after twenty-four hours, while the indirect effect was maximal later, namely forty-eight to sixty-six hours after the irradiation.

The results for the *spleen* demonstrated an indirect action of the irradiation. After irradiation of the lower abdomen, a reduction in weight of the spleen with central necrosis of the germinative zones in the white pulp was observed only when the adrenals were present (groups 5 and 6).

The *adrenals* were unaffected by the thymic irradiation with a small dose of radiation (group 3) but they increased significantly in weight after the intense irradiation of the lower abdomen to 40 mg. as compared with 31 mg. in the controls. Histologically the hypertrophy was confined to the cortex; the fascicular zone thickened, but the lipid globules were decreased, so much so that even an examination with the naked eye revealed the disappearance of the light yellow color of the normal gland.

When the head and neck were irradiated, the results were the same: adrenal hypertrophy and spleen atrophy in the normal animals (group 7) and no modification of the spleen in the adrenalectomized animals (group 8). The results for the thymus, reported in parentheses in the table, were complicated by the insufficient protection of this organ so that the combined effects of direct and indirect action of the rays were observed. Histological examination showed a straight, well defined line of demarcation between the anterior part of the gland receiving the direct impact of the rays and the posterior part which, at least in normal animals, showed signs of indirect action.

The *stomach* appeared very sensitive to an indirect action of the roentgen rays. Even in the animals receiving only a small exposure on the thymic region, there was

some degree of congestion. Sometimes hemorrhagic points or even well defined punched out-like ulcerations were found giving way to black spots or strings of clotted blood. All these were sometimes present in normal irradiated animals but most frequently in those without adrenals, and were obviously not due to the direct effect of the rays. The stomach was outside the zone of irradiation in all cases, and lesions of the gastric glands with disappearance of the principal (zymogenic) cells, as described after direct stomach irradiation by Regaud and Lacassagne[15] were not observed here.

Similar findings in the *intestine* were congestion, with also lesions in the lymphoid centers of the Peyer plates, after irradiation of the head and neck (groups 7 and 8). In the intestine directly in the path of the radiation (groups 5 and 6), specific lesions were observed in addition, such as destruction of the crypts of Lieberkühn, etc.[15]

As far as the *testis* was concerned, no indirect lesions were observed in the tubules. Fatty infiltration of the *liver* was very frequent in the normal irradiated rats but absent in the adrenalectomized animals after irradiation of either head or abdomen, as reported previously.[12]

DISCUSSION

The results showed conclusively that large doses of roentgen rays produced a secondary effect on organs distant from the area of irradiation, bearing chiefly upon the thymolymphatic system, the adrenals, the stomach, and the liver. The lesions thus found were similar to those found by Selye in various intoxications.[10,20]

The effects of roentgen rays on living tissues have been explained by the production through ionization of abnormal chemical compounds inside of the tissues (Failla, in ref. 4). These compounds, and more generally the products of cell disintegration, penetrate into the circulation to exert their toxic effects in the body. Loiseleur[13] was able to titrate abnormal protein fragments in the blood serum of irradiated men. One metabolite, resulting from protein fission and biologically very active, histamine, was observed in the blood of patients who had been irradiated[18] and it may play a rôle in the production of gastric lesions, especially in adrenalectomized animals.[16] More generally it seemed probable that the penetration of the products of cellular disintegration into the circulation produced the nonspecific signs of intoxication which are observed in the body after an intense local irradiation.[10]

Finally, the results made it possible to differentiate between the symptoms due to the direct impact of the roentgen rays and the secondary lesions of intoxication. The thymolymphatic atrophy was produced either by direct irradiation or by secondary factors. In the case of the testicular lesions, reported after the action of the roentgen rays,[15] they were not produced by the secondary intoxication. In the gastrointestinal tract, specific lesions were also differentiated from nonspecific (congestion resulting in ulceration), although the results did not preclude the possibility of ulcer formation by the direct impact of the rays. Finally, adrenal hypertrophy and fatty infiltration of the liver were not reported by careful observers after direct irradiation of either adrenals[3,5,15] or liver[15] but they were observed here as a secondary toxic effect of the roentgen rays.

SUMMARY

1. Large doses of roentgen rays produce a series of secondary symptoms in organs far distant from the point of impact, namely constant thymolymphatic atrophy and adrenal hypertrophy, and frequently fatty liver and ulcerations of the stomach. These lesions indicate the existence of a general intoxication following irradiation.

2. After adrenalectomy, the thymolymphatic atrophy and the fatty infiltration of liver produced by an intense localized irradiation are suppressed, but the gastric lesions and the general lethal effect of the rays are increased.

3. Thymolymphatic atrophy is also produced by the direct impact of roentgen

rays. Lesions of the testicular epithelium are exclusively produced by such direct effect.

REFERENCES

1. CREMIEU, R. Etude des effets produits sur le thymus par les rayons X. Medical thesis, Lyons, 1912.
2. DENIS, W., ALDRICH, M., and MARTIN, C. L. Study of relative toxic effects produced by regional radiation. *Am. J. M. Sc.*, 1920, *160*, 555–567.
3. DESJARDINS, A. U. Effect of irradiation on suprarenal gland. AM. J. ROENTGENOL. & RAD. THERAPY, 1928, *19*, 453–461.
4. DUGGAR, B. M. Biological Effects of Radiation. McGraw-Hill, New York, 1936.
5. FREY, HANS. Experimentelle Untersuchungen über die Röntgensensibilität der Nebennieren. *Acta radiol.*, 1928, *9*, 23–53.
6. HALL, C. C., and WHIPPLE, G. H. Roentgen-ray intoxication; disturbances in metabolism produced by deep massive doses of hard roentgen rays. *Am. J. M. Sc.*, 1919, *157*, 453–482.
7. HAMMER, J. A. Zur Histogenese und Involution der Thymusdrüse. *Anat. Anz.*, 1905–1906, *37*, 23; 41.
8. IMLER, A. E., and WAMMOCK, H. Vitamin B_1 in irradiation sickness. AM. J. ROENTGENOL. & RAD. THERAPY, 1940, *43*, 243–248.
9. JOLLY, J., and FERROUX, R. L'action nocive des rayons X sur les tissus vivants est-elle une action directe ou une action indirecte? *Compt. rend. Soc. de. biol.*, 1925, *92*, 67–70.
10. LEBLOND, C. P. Le syndrome non spécifique (réaction d'alarme de Selye). *Ann. d'endocrinol.*, 1939, *1*, 179–196.
11. LEBLOND, C. P., and SEGAL, G. Action des toxiques sur le thymus de l'animal sans surrénale. *Compt. rend. Soc. de biol.*, 1938, *129*, 838–840.
12. LEBLOND, C. P., NGUYEN-VAN THOAI, and SEGAL, G. Infiltration graisseuse du foie sous l'action des agents nocifs. *Compt. rend. Soc. de biol.*, 1939, *130*, 1557–1559.
13. LOISELEUR, J. Sur la mise en évidence d'une forme masquée de l'azote spécifique des états d'histolyse. *Bull. Soc. chem. biol.*, 1937, *19*, 1059–1081.
14. REGAUD, C., and CREMIEU, R. Sur l'involution du thymus produite par les rayons X. Résultats expérimentaux. Déductions therapeutiques. *Lyon méd.*, 1921, *118*, 5–20.
15. REGAUD, C., and LACASSAGNE, A. Effets histophysiologiques des rayons de Roentgen et de Becquerel-Curie sur les tissus adultes normaux des animaux superieurs. *Arch. Inst. du radium de l'Univ. de Paris*, 1927, *1*, 1–133.
16. ROSE, B., and BROWNE, J. S. L. Effect of adrenalectomy on histamine content of the tissues of the rat. *Am. J. Physiol.*, 1941, *131*, 589–594.
17. SCHWARZ, G. Ueber die Wirkung der Radiumstrahlen; eine physiologisch-chemische Studie am Hühnerei. *Arch. f. d. ges. Physiol.*, 1903, *100*, 532–546.
18. SEGAL, G. Variations du taux d'histamine chez des malades soumis à un traitement par rayons X. *Compt. rend. Soc. de biol.*, 1939, *131*, 1079–1080.
19. SEGAL, G., and LEBLOND, C. P. Réaction d'alarme produite par l'action des rayons X sur l'abdomen chez le rat. *Compt. rend. Soc. de biol.*, 1938, *129*, 279–281.
20. SELYE, H. Studies on adaptation. *Endocrinology*, 1937, *21*, 169–188.
21. WARREN, S. L., and WHIPPLE, G. H. Roentgen-ray intoxication. I. Unit dose over thorax negative—over abdomen lethal. Epithelium of small intestine sensitive to x-rays. *J. Exper. Med.*, 1922, *35*, 187–203.
22. WERNER, R. Zur chemischen Imitation der biologischen Strahlenwirkung. *München. med. Wchnschr.*, 1905, *52*, 691–693.

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FOREIGN BODY LOCALIZATION

AS PROVIDED WITH THE UNITED STATES ARMY TABLE UNIT

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WASHINGTON, D. C.

PRESENT conditions compel radiologists to give serious thought to the possibilities of their having to serve their country at least to the extent of adapting our specialty to the needs imposed by war. Roentgenological activities for this effort would be of an emergency character. No doubt, the bulk of the work would be roentgenoscopic. Many roentgenologists are inclined to consider foreign body localizations as the all-important function. In fact, when inquiring of those who had experience in World War I, the usual advice was that for field service we should provide merely for horizontal roentgenoscopy and for foreign body localizations. It was because of the strides which have been made in the field of roentgenology since that time, and the belief that the Army should be provided with equipment which would be serviceable in times of peace as well as in the event of war, that we insisted upon a much greater range of adaptation than necessary for these two functions.[3] Our equipment was not designed around working parts necessary for localization. The paramount consideration was to provide for roentgenoscopy with the patient in any position: lying, sitting or standing; to provide for general roentgenography as may be indicated in the more established hospitals; to provide for doing this work in a manner most convenient to the patient; to provide for one type of equipment to serve these needs in any hospital installation. It even appeared that roentgen therapy might be wanted in the theater of operations; the design of our roentgen machine unit permits this application. Modern methods of warfare seemed to demand such versatility of adaptation. Depending upon the tide of battle, in one locality a certain function might be required whereas in another locality time might not permit more than a limited degree of such service. We were certain that it would be cumbersome to depend upon special equipment for each type of function. We have sought to provide for quick action with equipment which can be easily disassembled and of which the component parts are of a weight no greater than two hundred pounds, thereby providing for portability. All small parts which might easily become detached and quickly lost have been eliminated.

Various methods of foreign body localization were considered for adaptation to the basic design of our equipment. The Strohl wire method and modifications of it were especially considered because the principles concerned with this method have been recognized so repeatedly by others.[1,2,4,5,6] However, in attempting to adopt this method, a number of shortcomings became apparent: (1) it requires independent movement of the roentgen tube with a stationary position of the fluoroscopic screen—a feature not conveniently accommodated when providing for the various positionings for roentgenoscopy, as already mentioned; (2) the depth calculations are based upon ratio relations of relatively small dimensions (i.e. the spacing of the wires or the diameter of an exit portal of a cone in relation to the position of the focal spot of the roentgen tube beneath the plane of either) and thereby minimal variations in the position of the focal spot of the roentgen tube or other variables would result in very appreciable errors; (3) the fluoroscopic screen is positioned either upon the skin surface or near to it,† thereby interfering with marking of

† With this method, it is necessary either to visualize wires through the density of the interposed part or to provide a "cut-off" of the field by means of a cone or diaphragm. With parts of

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the skin,* and (4) a number of small accessory parts are usually necessary—these being easily lost.

Less interest could be developed in other methods and therefore an entirely new method has been incorporated.† This method is based upon triangulation but it differs from the Strohl method in several respects: (1) with it, both the fluoroscopic screen and the roentgen tube are shifted; (2) spacing between the fluoroscopic screen and skin is allowable without incurring distortion of the alignment indicators, since with this method, the indicators are cross lines on the fluoroscopic screen, rather than wires or cone limits, beneath the patient; (3) large triangle relations are utilized, rather than small ratios, thus providing for lesser degrees of error in case of minimal variations, and (4) no small accessory parts are used—this new method depends upon a relatively fixed focal screen distance‡ (66 cm.) in relation to cross lines, inscribed into the fluoroscopic screen (spaced 22 cm. apart), plus the use of a skin marker and a localization scale, both of which are relatively large parts and are actually fixed to the main structure (see Fig. 1).

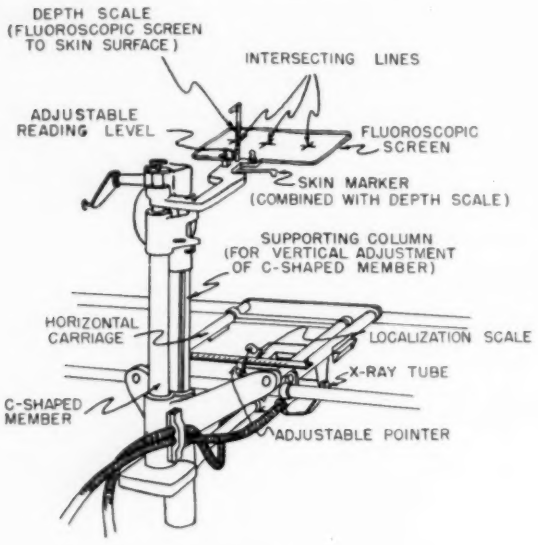

FIG. 1

Geometrically, the differences between the procedure followed with the Strohl method as compared with this new method might be diagrammed as in Figure 2.

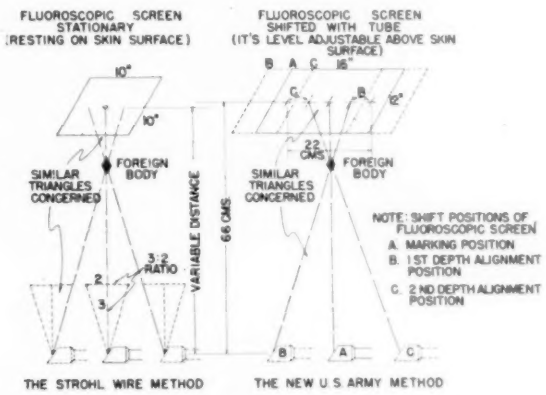

FIG. 2

With reference to Figures 1 and 3, the steps of procedure for this new method are as follows:

1. Check fixation locks on "C-shaped" member; secure alignment of focal spot to center of fluoroscopic screen.

2. Align a prominence on foreign body to intersection of central intersecting lines.

3. Dampen skin marker pad with tincture of iodine or ink and adjust it to this alignment (foreign body and intersection of central intersecting lines); lower skin marker pad, until it rests on the skin, thereby marking it.

4. Read distance between fluoroscopic screen and skin by way of scale on depth marker (Fig. 3, *A*).

considerable thickness, the secondary radiation produced within the interposed part, obscures the detail either of outline of the wires or of the proper limits of the primary beam. This unsharpness of detail is made worse by positioning the fluoroscopic screen at any distance above the skin surface.

* During the last war a perforation was provided in the center of the fluoroscopic screen to permit insertion of a screen marker. The result was that a very conscientious roentgenologist, who would make alignments by viewing as nearly as possible directly over the perforation, would unjustly receive primary or secondary radiation whereas a less conscientious roentgenologist would be spared this exposure.

† Credit is acknowledged to Technical Sergeant Lawrence F. Black, to Staff Sergeants Roy Day and Herbert Fox for their constructions of preliminary models.

‡ The fluoroscopic screen and tube can be moved vertically, over a range of 7 inches when the C-shaped member supporting them is in position for horizontal roentgenoscopy, as used for foreign body localization.

5. Shift tube and fluoroscopic screen so as to align the same prominence of the foreign body, as considered in step 2, to the intersection of either of the outer intersecting lines (Fig. 3, *B*).

6. Slide localization scale and adjust pointer to the centimeter value coinciding with the centimeter distance between the fluoroscopic screen and the skin as measured in step 4; this is the arbitrary zero; clamp cuff for fixation of pointer to side rail of table.

7. Slide roentgen tube and fluoroscopic screen in direction opposite to that used in step 5, above, until the same prominence on the foreign body becomes aligned to the intersection of the opposite outer intersecting lines (Fig. 3, *C*).

8. Read on localization scale the depth of foreign body beneath the skin.

The calibrations on the localization scale (which is positioned on the outer members of the horizontal carriage—see Fig. 1) were determined by way of the following geometric analysis (Fig. 4):

1. *AB* equals the spacing between the outer intersecting lines; it is equal to 22 cm.

2. *FS* equals the focal-screen distance (focal spot to intersection of central intersecting lines); it is equal to three times *AB*, or 66 cm. (plus or minus minor deviations in the position of the focal spot).

3. If a foreign body were located at *S* (i.e., just beneath the intersection of the central intersecting lines), for alignments of it to the intersection of the outer intersecting lines at *A* and then at *B*, the roentgen tube would have to be moved with the fluoroscopic screen for distances equal to *SA* and then *SB*, respectively.

On the localization scale the distances of such movements would be represented by *FC* and *FD*, since the gradations on this scale are limited to a total range of 22 cm. (i.e. the same as the spacing between the outer intersecting lines described upon the fluoroscopic screen). In the case of foreign bodies located at other levels below the plane *AB*, this same ratio relationship would hold true with respect to the distance of shifting requirement and the distance between the focal spot of the roentgen tube and the foreign body. Similar triangles are involved and since the ratio relationship between *AB* and *FS* is as 1 is to 3, for foreign bodies located at any level beneath the

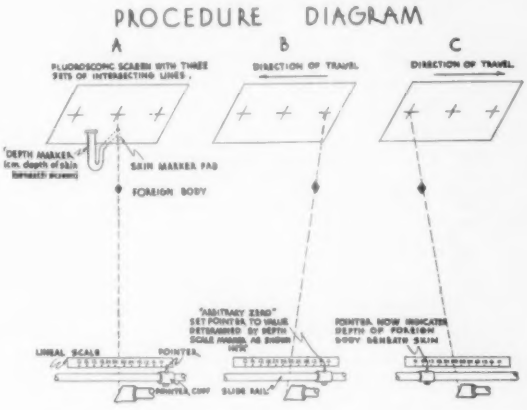

Fig. 3

fluoroscopic screen and between it and the roentgen tube, the distance of shift required for similar alignments would equal one-third of the distance between the plane of the focal spot and the plane of the foreign body. Actually, the measurement between the focal spot and the foreign body is unimportant. Instead, the important measurement is that between the level of the fluoroscopic screen and the foreign body. This measurement can be estimated by calculation not of the distance of shift required for the alignments, described above, but instead by calculating on the basis of the difference between that distance and the extreme range of shifting possibility, i.e. the 22 cm. Thus the calculation as to the depth of the foreign body beneath the plane of the fluoroscopic screen is based upon the "untraveled distance." This can be explained as follows:

4. Since triangle *EJG* is similar to triangle *JHI*, the distance *SJ* bears the same ratio relationship to *HI* as does *JF* to *EG*, that is a 3 to 1 ratio.

5. *HI* is equal to *HS* plus *SI*.

6. *HS* equals *GD* while *SI* equals *CE*;

therefore *HI* equals *CE* plus *GD*. *CE* plus *GE* is the untraveled distance (22 cm. minus the distance of shifting of the roentgen tube and fluoroscopic screen).

7. The distance between the fluoroscopic screen to the skin is subtracted by making

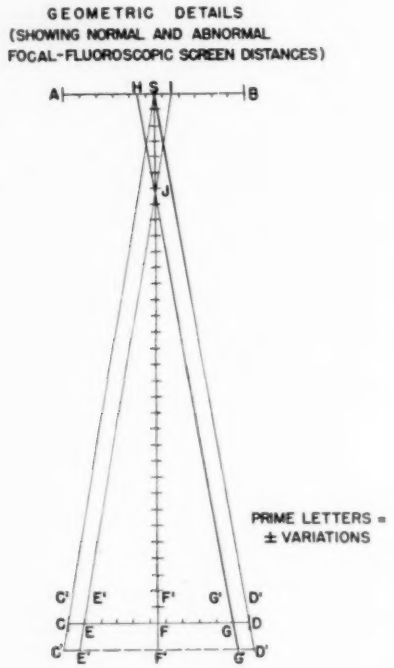

FIG. 4

the adjustment of the pointer to an "arbitrary zero" as shown in the diagram *B* of Figure 3 and as described in step 6 concerned with the outline of procedure, described above. Therefore, the reading of the untraveled distance (as indicated on the localization scale) indicates the measurement of depth of the foreign body beneath the skin level.

It can be anticipated that roentgen tubes will have to be changed and that there may be variations in the position of their focal spot with respect to the fluoroscopic screen. Certainly it would be impractical to have to accurately adjust each roentgen tube or the fluoroscopic screen with every change-over. Mention has already been made that, with this method, the ratio relations of relatively large triangles are utilized. Analysis as to the extent of error which might result because of variations in the focal-fluoroscopic screen distance is therefore presented (Fig. 4).

EG represents the distance of shifting required for the alignments of a foreign body at $\mathcal{J}$, first in relation to the intersection at *A* and then at *B*.

Ideally (i.e. when the focal screen distance is exactly 66 cm.):

$$EG:F\mathcal{J}::CD:FS.$$

$$EG\times FS=CD\times F\mathcal{J}$$

therefore

$$EG=\frac{CD\times F\mathcal{J}}{FS}.$$

Substituting:

$$EG \text{ (the distance of shifting required)} = \frac{22\times F\mathcal{J}}{66} \text{ or } \frac{F\mathcal{J}}{3}. \qquad (1)$$

Abnormally:

Plus or minus variations with respect to the position of the focal spot of the roentgen tube in relation to 66 cm. will result in plus or minus variations in the value of *FS* and also in the value of $F\mathcal{J}$. These new distances might be considered as $F'S$ and $F'\mathcal{J}$, respectively. With this consideration, the above geometric analysis is modified as follows:

$$E'G':F'\mathcal{J}::C'D':F'S$$

$$E'G'\times F'S=C'D'\times F'\mathcal{J}.$$

Therefore:

$$E'G'=\frac{C'D'\times F'\mathcal{J}}{F'S}.$$

Substituting:

$$E'G'=\frac{22\pm\times F\mathcal{J}\pm}{66\pm}. \qquad (2)$$

Comparing the requirement of shifting of the tube, under ideal conditions versus the requirement under abnormal conditions, these two formulae (1) and (2) indicate that with the expected limits in deviation in po-

sition of the focal spots of no greater than 1.5 cm., these conclusions (1) and (2) would practically be resolved to:

$$\text{shifting distance} = \frac{FJ}{3} \text{ versus } \frac{FJ \pm 1.5}{3 \pm 1.5}$$

Ideally: Abnormally:

Such variations will be found to amount to no more than a few millimeters.

After working with a number of these table units, at various times, it became apparent that variables other than the focus-fluoroscopic screen distance must be compensated. During hot and humid weather, the bakelite support of the fluoroscopic screen may buckle; the fluoroscopic screen itself may develop corrugations of its surface. Moreover, one examiner may make his alignments by perpendicular viewing whereas another examiner may make his alignments in a more tangential manner. Therefore, parallax must be considered. Thought was even given to the possibility of the difference in effect of penumbra with consideration of the effective focal spot dimensions concerned with the two alignments. Errors due to these factors were found to be relatively small, amounting to no more than 5 mm. in the depth calculations; however, it seemed important that the method itself should be entirely accurate. Otherwise, it can be expected that the utmost effort would not be exercised toward care and precision in the technical procedure. Therefore, it was decided to incorporate an adjustable reading level for the depth scale marker* (see Fig. 1) in order to counteract the mal-effects of these otherwise more or less uncontrollable variables—variables common to any roentgenoscopic method.

Though proper construction features and relations are provided as the equipment leaves the factory, instructions are given in our supplemental manual for roentgenologists (TM 8–275) that a preliminary testing of the adjustment be made. This testing should serve a two-fold purpose; it should orient the roentgenologist as to the steps concerned and it should provide for compensation against the several variables mentioned; changes due to the elements and variations in individual applications.

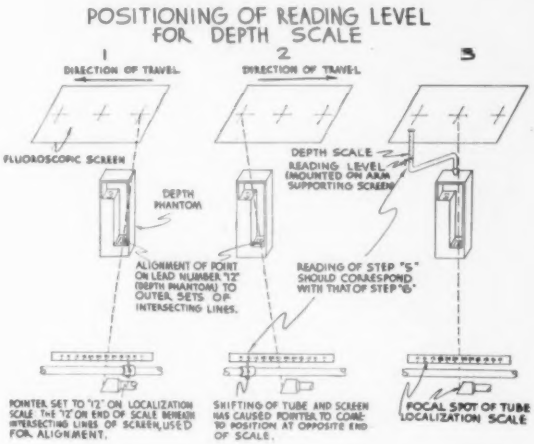
POSITIONING OF READING LEVEL FOR DEPTH SCALE
1
2
3
DIRECTION OF TRAVEL
DIRECTION OF TRAVEL
FLUOROSCOPIC SCREEN
DEPTH PHANTOM
DEPTH SCALE READING LEVEL (MOUNTED ON ARM SUPPORTING SCREEN)
ALIGNMENT OF POINT ON LEAD NUMBER "12" (DEPTH PHANTOM) TO OUTER SETS OF INTERSECTING LINES.
READING OF STEP "5" SHOULD CORRESPOND WITH THAT OF STEP "6"
POINTER SET TO "12" ON LOCALIZATION SCALE. THE "12" ON END OF SCALE BENEATH INTERSECTING LINES OF SCREEN, USED FOR ALIGNMENT.
SHIFTING OF TUBE AND SCREEN HAS CAUSED POINTER TO COME TO POSITION AT OPPOSITE END OF SCALE.
FOCAL SPOT OF TUBE
LOCALIZATION SCALE

FIG. 5

This preliminary testing is accomplished with the use of a depth phantom. Arbitrarily, only two levels have been selected: a 3 cm. level and a 12 cm. level and lead numbers have been positioned accordingly. The procedure concerned with this preliminary testing as indicated in Figure 5, is as follows:

1. Place a board across the litter (table top) to provide for a rigid surface (comparable to the patient) and on this board, 4 or 5 cm. beneath the fluoroscopic screen, place the depth phantom in position so that the lead letters are on planes which respectixely represent their distances below the top surface of the phantom.

2. Align one conspicuous point of the number "12" to either of the two outer intersecting lines of the fluoroscopic screen.

3. Adjust the pointer on the horizontal rail and clamp it to a position so that it points to "12" on the localization scale, this adjustment being made to the "12" on the end of the localization scale coinciding

* Appreciation is expressed for the scrupulous cooperation on the part of the Westinghouse X-Ray Division and in particular to Mr. C. V. Aggers, Mr. O. C. Holstein and Mr. J. R. Edelen, for their studies of these phases of our problem and their incorporating the adjustable reading level into all of our table units.

with that of the intersecting lines selected for the alignment of the lead number "12" of the depth phantom.

4. Shift the tube and the screen in the opposite direction until the very same point of the lead number "12" of the depth

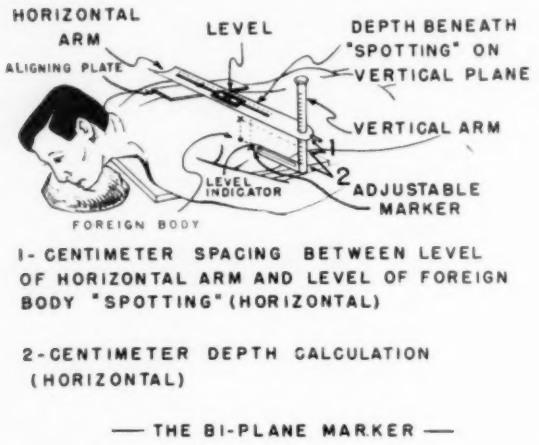

FIG. 6

phantom is aligned to the opposite outer intersecting lines of the fluoroscopic screen.

5. Read the new value indicated on the localization scale by the pointer on the horizontal carriage. Keep this value in mind.

6. Shift the fluoroscopic screen and roentgen tube to a position for alignment of the lead number "12" (of the phantom) to the central set of intersecting lines. Superimpose the skin marker into this alignment and lower the depth scale until the skin marker rests upon the top surface of the depth phantom. Read the value indicated on the depth scale—the indicated depth of the top of the phantom (substituting for the skin surface) beneath the fluoroscopic screen.

7. In case the "depth scale value," indicated in step 6, above does not coincide with the value indicated in step 5, above, release the set screw concerned with the reading level (as shown in Fig. 1) and readjust the reading level to the value indicated in step 5.

The accuracy of this adjustment should then be doubly checked by proceeding with a localization of the lead number "3" or the lead number "12," following the outline with reference to Figure 3, above. If the results obtained do not exactly coincide with the true depth values for these lead numbers, a second checking as to proper positioning of the reading level should be accomplished, as just described. These preliminary testings should be repeated, backward and forward, until the calculations are consistently accurate.

After becoming acquainted with the procedure, in this manner, actual localizations can be accomplished within a time limit of 30 to 45 seconds. Very little roentgen radiation exposure of the patient should be necessary. At the most it should not exceed 140 milliampere-seconds. The very worst conditions would be using the shortest focal-skin distance, which, allowing for a 4 inch sag of the litter, would be 10 inches. Even then the exposure received by the patient should not exceed 15 r.

There have been some advocates of biplane roentgenoscopy. Surgeons are especially prone to speak of this need. They want an indication of the foreign body in two planes.

Biplane roentgenoscopy was not considered practical for this unit for several reasons: (1) it would have required the use of two tubes and two fluoroscopic screens or readjustments of the one tube or screen—a costly provision, in weight, expenditure or time; (2) small foreign bodies cannot be adequately visualized through dimensions such as the width of the chest or trunk; (3) where many fragments are to be localized, double markings are too likely to lead to confusion, and (4) such a procedure would require double or more than double the roentgen radiation exposures upon the patient, with a concurrent increase in the secondary radiation exposure upon the operator.

In lieu of such a provision there has been developed a biplane marker. This marker is an accessory item, not a component part of the table unit. It can be used at any time. It does not require roentgenoscopic visualization. It consists of a horizontal level-

ing arm with an adjustable marker which slides on a vertical supporting arm. Centimeter gradations are etched upon this latter arm thereby providing for positioning the marker at the depth level calculated by the localization procedure described above. If the horizontal leveling arm rests upon a level which is higher than the level at which the foreign body was spotted, the marker can first be used to measure the difference in these two levels; the difference (measured in centimeters) then added to the depth calculation value thereby indicating the proper level for positioning the marker. The second marking (i.e. in the vertical plane) is accomplished by simply sliding the horizontal arm, with the adjustable marker properly positioned, until the latter comes in contact with the skin surface. Thereafter, the depth of the foreign body beneath the new marking can be calculated by reading on the horizontal arm the value of the gradation scale which is superimposed in alignment with the first "spotting," as accomplished on the skin surface of the horizontal plane (Fig. 6).

SUMMARY

The designing of field roentgenologic equipment has been guided particularly by the requirements for roentgenoscopy with the patient lying, sitting or standing. A new method of foreign body localization has been provided. The geometric principles of this method are compared with those of the Strohl wire method or its modifications. Since the ratio relations of relatively large triangles are utilized in the application of our method as compared with the smaller triangle relations which govern the calculations by the Strohl method, it is believed that basically this new method provides for a greater degree of accuracy than provided by the Strohl method. Errors due to variations in position of the focal spot of the roentgen tube are discussed; geometric calculations indicate that they would be inappreciable. Other "uncontrollable variables" such as warping of the bakelite support for the fluoroscopic screen, corrugations in the screen itself, as might be expected in hot weather, and parallax are cited. To compensate for all of these, an adjustable reading level has been incorporated. This provides for subtracting the plus or minus errors by including them with the value of the spacing between the skin and the fluoroscopic screen. The method thus provides for a direct and basically accurate calculation of depth—a calculation as to depth, not beneath the level of the fluoroscopic screen as is usually considered, but actually beneath the surface of the skin of the patient. The localization procedure should require less than forty-five seconds and the roentgen-radiation exposure received by the patient should not exceed 15 roentgens. Mention is made of an accessory item, a biplane marker, which serves to mark the skin in the vertical plane, thus providing for two-plane localizations as might be accomplished by biplane roentgenoscopy.

REFERENCES

1. Howard, C. Tube tilt method of localization of foreign bodies. Am. J. Roentgenol. & Rad. Therapy, 1941, *45*, 121–123.
2. Gilbert, R. J., and Hertenstein, H. U. Contribution to the localization of foreign bodies. Am. J. Roentgenol. & Rad. Therapy, 1941, *45*, 768–773.
3. de Lorimier, A. A. Wartime military roentgenology. *Radiology*, 1941, *36*, 391–403.
4. Reid, E. K., and Black, L. F. Foreign body localization in military roentgenology. *Radiology*, 1938, *31*, 567–583.
5. Strohl. Procédé simple pour localiser rapidement des projectiles par la radioscopie. *J. de radiol. et d'électrol.*, 1916–1917, *2*, 172–173.
6. United States Army X-Ray Manual. First Edition. Paul B. Hoeber, Inc., New York, 1918. Second edition, 1932.

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Representatives on American Board of Radiology: Douglas Quick, New York, N. Y., R. H. Stevens, Detroit, Mich., B. P. Widmann, Philadelphia, Pa.

Twenty-seventh Annual Meeting: Atlantic City, N. J., June 8–9, 1942.

EDITORIAL

THE VALUE OF COOPERATION BETWEEN THE ROENTGENOLOGIST AND THE GASTROSCOPIST

THE introduction of any new method of examination may be fraught with considerable handicaps and difficulties and the introduction of gastroscopy as a diagnostic procedure was no exception to the rule. It was not until 1932 when Schindler, Henning and Wolf perfected the flexible gastroscope that much interest was taken in this type of examination and its popularity began to increase. Before this time the method presented considerable technical difficulties to the gastroscopist and its use was not without danger to the patient. These objectionable features have now for the most part been removed, and in the hands of an experienced and skillful operator gastroscopy is no longer accompanied by the dangers that beset the use of the more rigid type of gastroscope.

With the perfection of the more flexible type of gastroscope there was an unfounded belief among some workers that this device would supplant the use of roentgen ray in the examination of the stomach, or if it did not entirely supplant it, that the gastroscope would prove a healthy rival. We now know from experience that "this idea is without foundation, as the two methods, far from being competitive, are complementary to each other."[1] During these many years it has been possible with the roentgen ray to demonstrate the form, the contour and the relief of the stomach as well as the type and character of the peristalsis, and the emptying time of the stomach can be studied, whereas by the use of the gastroscope the finer characteristics of the mucosa of the stomach may be observed and note made not only of the color but of the type of mucosa present.

Since the brilliant work of Forssell in his studies of the normal and pathological appearances of the gastric mucosa demonstrated roentgenologically, there has been an intensive study of the finer details of the gastric mucosa by means of the roentgen ray; not only can these be observed roentgenoscopically but many workers have devised ingenious pieces of apparatus for a roentgenographic recording of the mucosal relief appearances. It is now possible by roentgenological methods to demonstrate not only the gross features of the mucosal folds such as their width, direction and to some extent their elasticity, but abnormalities in the mucosa can be recognized. But the gastroscopist with his more direct vision of the interior of the stomach has a better opportunity to study the finer details of the mucosa than has the roentgenologist. There are, however, certain portions of the stomach which it is difficult or impossible to visualize by means of the gastroscope, namely the cardiac orifice, the highest part of the lesser curvature, a small part of the posterior wall, the most medial part of the fundus and the lowest part of the greater curvature. It is with considerable difficulty that the cardiac orifice is visualized because of the close proximity of the mucosa to the optic. Moreover, suspected lesions in the cardiac end of the stomach should not be gastroscoped because of the attendant danger of perforation.

[1] Davidson, S. W., and Rose, J. D. The value of co-operation between the radiologist and the gastroscopist. *Brit. J. Radiol.*, 1941, *14*, 307–319.

Davidson and Rose call particular attention to the value of cooperation between the roentgenologist and the gastroscopist and they discuss the attendant difficulties of diagnosis of certain lesions by either method of study and emphasize that only by a combined method may the best results and more accurate diagnoses be arrived at.

In this number of the JOURNAL will be found a report by Templeton and Boyer[2] on the diagnosis of gastric cancer, an analysis of the gastroscopic and roentgenologic findings. Their study is based upon an analysis of 189 cases selected from 1,072 patients examined by both gastroscopy and roentgenology. They quite properly point out that the discrepancies which occur between the findings of the gastroscopist and those of the roentgenologist, aside from inherent differences in the two diagnostic methods, vary according to the examiners' experience, dexterity and opinions. They emphasize the need of close collaboration between the roentgenologist and the gastroscopist and the importance of either the roentgenologist or the gastroscopist having knowledge of the other's findings. The nebulous findings of one examiner are often confirmed by the other, once the location of the suspected lesion is known in which the second examiner may institute certain maneuvers and positions which are ordinarily omitted in the routine examination of the patient. Their study, primarily on the diagnosis of gastric cancer, was not to establish a relative efficiency of one method over the other but to show that the accuracy of the diagnosis obtained by using both methods is greater than that obtained by using only one.

From a careful analysis of all the available data, Templeton and Boyer draw certain important conclusions, namely, that in most instances a gastric cancer visible by one method is demonstrable by the other and will be diagnosed accurately by both the gastroscopist and the roentgenologist; that certain lesions by their very nature and location may be visible to the gastroscopist and not to the roentgenologist, and vice versa; that the differentiation between benign and malignant lesions by both methods is not always easy and that the interpretation of the roentgenologist in these doubtful cases will be just as correct as is that of his colleague, the gastroscopist.

In another article in this issue of the JOURNAL, by Benedict,[3] the importance of the gastroscope in association with roentgen studies in cases where hemorrhages occur without demonstrable gastric or duodenal lesions is discussed.

The importance of having a roentgenological examination prior to the gastroscopy is emphasized by all workers.

The observations of these various authors suggest the necessity of close cooperation between the gastroscopist and the roentgenologist and as a result of this teamwork a marked increase in the percentages of correct diagnoses of lesions of the stomach will follow.

[2] Templeton, F. E., and Boyer, R. C. The diagnosis of gastric cancer; an analysis of the gastroscopic and roentgenologic findings. AM. J. ROENTGENOL. & RAD. THERAPY, Feb., 1942, *47*, 262–274.

[3] Benedict, E. B. Hemorrhage from gastritis; report based on pathological, clinical, roentgenological and gastroscopic findings. AM. J. ROENTGENOL. & RAD. THERAPY, Feb., 1942, *47*, 254–261.

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

Items for this section solicited promptly after the events to which they refer.

MEETINGS OF ROENTGEN SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. H. Dabney Kerr, University Hospital, Iowa City, Iowa. Annual Meeting: Atlantic City, N. J., Oct. 6–9, 1942.

American College of Radiology
Secretary, Mac F. Cahal, 540 N. Michigan Ave., Chicago, Ill. Annual meeting: Atlantic City, N. J., June 10, 1942.

Section on Radiology, American Medical Association
Secretary, Dr. J. T. Murphy, 421 Michigan St., Toledo, Ohio. Annual meeting: Atlantic City, N. J., June 8–12, 1942.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y. Annual meeting, 1942: To be announced.

Radiological Section, Baltimore Medical Society
Secretary, Dr. Walter L. Kilby, Baltimore. Meets third Tuesday each month, September to May.

Section on Radiology, California Medical Association
Secretary, Dr. J. D. Coate, 434 Thirtieth St., Oakland, Calif.

Radiological Section, Connecticut Medical Society
Secretary, Dr. Max Climan, 242 Trumbull St., Hartford, Conn. Meets bi-monthly on second Thursday, at place selected by Secretary. Annual meeting in May.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. H. W. Ackemann, 321 W. State St., Rockford, Ill.

Radiological Section, Los Angeles County Medical Association
Secretary, Dr. Donald R. Laing, 65 North Madison Ave., Pasadena, Calif. Meets on second Wednesday of each month at the County Society Building.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Brooklyn Roentgen Ray Society
Secretary, Dr. Leo Harrington, 880 Ocean Ave., Brooklyn, N. Y. Meets monthly on fourth Tuesday, October to April.

Buffalo Radiological Society
Secretary, Dr. Joseph S. Gian-Francheschi, 610 Niagara St., Buffalo, N. Y. Meets second Monday of each month except during summer months.

Chicago Roentgen Society
Secretary, Dr. C. J. Challenger, 3117 Logan Blvd. Meets second Thursday of each month October to April inclusive at the Palmer House.

Cincinnati Radiological Society
Secretary, Dr. J. E. McCarthy, 707 Race St., Cincinnati, Ohio. Meets third Tuesday of each month, October to May, inclusive.

Cleveland Radiological Society
Secretary, J. O. Newton, 13921 Terrace Rd., East Cleveland. Meets at 6:30 P.M. at Midday Club on fourth Monday each month, October to April, inclusive.

Denver Radiological Club
Secretary, Dr. Edward J. Meister, 366 Metropolitan Bldg., Denver, Colo. Meets third Friday of each month at Denver Athletic Club.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. E. R. Witwer, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

Florida State Radiological Society
Secretary, Dr. Walter A. Weed, 204 Exchange Bldg., Orlando, Florida. Meetings in May and November.

Georgia Radiological Society
Secretary, Dr. R. C. Pendergrass, Prather Clinic Bldg., Americus, Ga. Meets in November and at annual meeting of Medical Association of Georgia in the spring.

Radiological Society of Greater Kansas City
Secretary, Dr. P. E. Hiebert, 811 Huron Bldg., Kansas City, Kansas. Meets third Thursday of each month at a place designated by the president.

Illinois Radiological Society
Secretary, Dr. Wm. DeHollander, St. John's Hospital, Springfield, Ill. Meets three times a year.

Indiana Roentgen Society
Secretary, Dr. H. C. Ochsner, Methodist Hospital, Indianapolis. Meeting held the second Sunday in May annually.

Kentucky Radiological Society
Secretary, Dr. W. C. Martin, 321 W. Broadway, Louisville. Meets annually in Louisville on first Saturday in April.

Long Island Radiological Society
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:30 P.M.

Louisiana Radiological Society
Secretary, Dr. J. R. Anderson, 1130 Louisiana Ave., Shreveport. Meets annually during Louisiana State Medical Society meeting. Next meeting New Orleans, April, 1942.

Michigan Association of Roentgenologists
Secretary, Dr. E. M. Shebesta, 1429 David Whitney Bldg., Detroit. Three meetings a year, Fall, Winter, Spring.

Milwaukee Roentgen Ray Society
Secretary, Dr. I. I. Cowan, Mt. Sinai Hospital, Milwaukee, Wis. Meets monthly on first Friday at University Club.

Minnesota Radiological Society
Secretary, Dr. J. P. Medelman, 572 Lowry Medical Arts Bldg., St. Paul.

Nebraska Radiological Society
Secretary, Dr. D. A. Dowell, Medical Arts Bldg., Omaha, Nebr. Meets third Wednesday of each month, at 6 P.M. at either Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. Hugh F. Hare, Lahey, Clinic, Boston, Mass. Meets monthly on third Friday, Boston Medical Library.

Radiological Society of New Jersey
Secretary, Dr. H. J. Perlberg, 921 Bergen Ave., Jersey City. Meets annually at time and place of State Medical Society. Mid-year meetings at place chosen by president.

New York Roentgen Society
Secretary, Dr. Paul C. Swenson, Presbyterian Hospital, New York City. Meets monthly on third Monday, New York Academy of Medicine, at 8:00 P.M.

North Carolina Roentgen Ray Society
Secretary, Dr. Major Fleming, Rocky Mount, N. C. Annual meeting at time and place of State Medical Society. Mid-year scientific meeting at place designated.

North Dakota Radiological Society
Secretary, Dr. L. A. Nash, St. John's Hospital, Fargo. Meetings held by announcement.

Central New York Roentgen Ray Society
Secretary, Dr. C. F. Potter, 820 S. Crouse Ave., Syracuse. Three meetings a year. January, May, November.

Ohio Radiological Society
Secretary, Dr. J. E. McCarthy, 707 Race St., Cincinnati. Meets at time and place of annual meeting of Ohio State Medical Association.

* Secretaries of Societies not here listed are requested to send the necessary information to the Editor.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. L. E. Wurster, 416 Pine St., Williamsport.

Philadelphia Roentgen Ray Society
Secretary, Dr. B. R. Young, Temple University Hospital. Meeting first Thursday of each month from October to May inclusive at 8:15 P.M., in Thompson Hall, College of Physicians, 19 S. 22d St.

Pittsburgh Roentgen Society
Secretary, Dr. H. W. Jacox, 4800 Friendship Ave. Meets second Wednesday each month, 4:30 P.M., October to June, Pittsburgh Academy of Medicine.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. S. C. Davidson, 277 Alexander St. Meets on second Thursday from October to May, inclusive. 8 P.M., Rochester Academy of Medicine Building.

Rocky Mountain Radiological Society
Secretary, Dr. A. M. Popma, 220 N. First St., Boise, Idaho, Annual meeting in Denver, summer of 1942.

St. Louis Society of Radiologists
Secretary, Dr. W. K. Mueller, University Club Bldg. Meets fourth Wednesday of October, January, March and May, at a place designated by the president.

San Francisco Radiological Society
Secretary, Dr. H. A. Hill, 450 Sutter St., San Francisco. Meets monthly on third Thursday at 7:45 P.M., first six months at Toland Hall, second at Lane Hall.

South Carolina X-Ray Society
Secretary, Dr. T. A. Pitts, Baptist Hospital, Columbia, S. C. Meets in Charleston on first Thursday in November, also at the time and place of South Carolina State Medical Association.

Tennessee Radiological Society
Secretary, Dr. F. B. Bogart, 311 Medical Arts Bldg., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. L. W. Baird, Scott and White Clinic, Temple, Texas. Next annual meeting, Houston, Texas, February 7, 1942.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets every Thursday from 4:00–5:00 P.M., Room 301, Service Memorial Institute.

Virginia Radiological Society
Secretary, Dr. C. H. Peterson, 603 Medical Arts Bldg., Roanoke, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. K. J. Holtz, American Bank Bldg., Seattle. Meets fourth Monday each month, College Club, Seattle.

X-ray Study Club of San Francisco
Secretary, Dr. J. M. Robinson, University of California Hospital. Meets monthly in evening on third Thursday.

Cuba

Sociedad de Radiología y Fisioterapia de Cuba
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

British Empire

British Institute of Radiology Incorporated with the Röntgen Society
Meets monthly on third Thursday from November to June inclusive, at 8:15 P.M., 32 Welbeck St., London.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets on the third Friday of each month during the winter at 8:15 P.M. at the Royal Society of Medicine 1, Wimpole St., London, W. 1.

Faculty of Radiologists
Secretary, Dr. M. H. Jupe, 32 Welbeck St., London, W. 1 England.

Section of Radiology and Medical Electricity, Australasian Medical Congress.
Secretary, Dr. H. M. Cutler, 139 Macquarie St., Sydney, New South Wales.

Radiological Section of the Victorian Branch of the British Medical Association
Secretary, Dr. Keith Hallam, St. George's Hospital, K.E.W., Melbourne, E. 4, Victoria, Australia. Meets monthly from March to November inclusive.

Canadian Association of Radiologists
Secretary, Dr. A. D. Irvine, 540 Tegler Bldg., Edmonton, Alberta.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N.S.

Radiological Section, New Zealand British Medical Association
Secretary, Dr. Colin Anderson, Invercargill, New Zealand. Meets annually.

Continental Europe

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7. Madrid, Spain. Meets monthly in Madrid.

Société Suisse de Radiologie (Schweizerische Röntgen-Gesellschaft)
Secretary for French language, Dr. A. Grosjean La Chaux de Fonds.
Secretary for German language, Dr. Scheurer, Molzgasse Biel. Meets annually in different cities.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banul Mărăcine, 30, S. I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad, USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Leningrad Roentgen Ray Society
Secretaries, Drs. S. G. Simonson and G. A. Gusterin. Meets monthly, first Monday at 8 o'clock State Institute of Roentgenology and Radiology, Leningrad.

Moscow Roentgen Ray Society
Secretaries, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevskv. Meets monthly, first Monday, 8 P.M.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

BULLETIN OF THE AMERICAN COLLEGE OF RADIOLOGY

The following article is of such pertinent interest to radiologists that the American College of Radiology has obtained permission to reprint it from the *Journal of the Michigan State Medical Society*, in which it first appeared.

THE RELATIONSHIP OF THE ROENTGENOLOGIST TO THE PHYSICIAN AND SURGEON*

By Leon M. Bogart, M.D.
Flint, Michigan

Leon M. Bogart, M. D.

M.D., Chicago College of Medicine and Surgery, 1913; Chief of Surgery at St. Joseph Hospital, Flint, Michigan; president-elect of Flint Academy of Surgery; member, Michigan State Medical Society; member, American Association for the Study of Goiter.

Roentgen, when he discovered the x-ray in 1895, uncovered a hornet's nest. The doctor, secure in his fringe of scientific terms, was too close to the aura of empiricism to be jolted out of his toppling Galenic conception. Keen's "Surgery," published in the latter part of the 19th century, spoke of cholecystitis as being caused by tight lacing, but spoke very little of the disease itself. Tait, in the late seventies of the 19th century, doubted the wisdom of asepsis in surgery. Osler's edition of 1905 has little reference to x-rays. Surgeons abroad early recognized its value, for in 1896 reports of surgical pathological lesions were described with x-ray findings. In 1907, in Dr. DaCosta's "Surgery," little reference was made to x-ray in the text, but in a discussion rather extensive mention is made of possibilities, also the advisability of mixing bismuth with food to visualize the gastro-intestinal tract was discussed.

The mysterious ray, piercing the depth of tissues and recording different density, not only brought out the silhouette of bone, but emphasized the necessity of physical comparison of shadows in physiology as well as pathology. When Cannon and Williams first gave an opaque meal, the innermost secrets of eternally covered unknowns were blasted open to the curious gaze of the delving scientists, as though it were the secrets of the solid undercore of the earth made available for scientific observation. When early reports of x-ray burns and x-ray epithelioma became known, the destruction of the tissues became a hunting ground for the investigator and research worker, to turn the flood of destruction to the nihilist cell—the cancer cell.

From the little flicker of the first gas jet vacuum tube emitting the unknown ray that man made and controlled, grew the precise tabulator of pathological processes of today.

Friedenwald, many years ago, brought to the attention of the roentgenologist the irregularity of the mucosa in gastric ulcer, and now this sign is coming into prominence with the improvement of the technique of rugae visualization. The laboratory evaluation of gastric ulcer diagnosis has been greatly superseded by the x-ray findings, but here the surgeon must remember that often one is apt to read into the plate nonexistent pathology.

It is indeed a far cry from the full hour exposure required in the early days of x-ray to the present split second exposure with its exact delineation and clarity. The art of physical diagnosis and great personal error has largely given way to the penetrating ray. Yet we, as physicians and surgeons, by relying too much upon the trained interpretation of the x-ray findings, must not lose sight that the personal equation is not to be discounted, for the radiologists differ between themselves just as frequently as the physicians or surgeons. The plate is inanimate—the human mind reads its signs.

One of the most useful branches of radiologic technic, and one probably requiring most judgment, fluoroscopy has lent itself to be the most blatant instrument of the charlatan. Newspaper and radio advertisements are full of misconceptions of fluoroscopic values and the public is misled as to its possibilities. All of us, I am sure, deplore its misuse and hope the public can be educated to its limitations.

The importance of the x-ray in the diagnosis of tuberculosis and as a check-up of its therapeutics has been proved invaluable. The detection of metastases and emboli is another chapter of scientific detection greater than fiction. Of course the oldest service for which x-ray was used was the diagnosis of bone pathology and perhaps it is the one fraught with the most danger to the surgeon, because of the perfection expected in the treatment of fractures. The measurements and comparisons which the student of yore was taught are entirely disregarded by him now, yet in my judgment not to be discarded, for if length, alignment and natural

* Read first March 18, 1939, before the Michigan State Roentgenological Society, Hurley Hospital, Flint, Michigan.

Read again by request May 21, 1941, before the Third Annual Fracture Clinic, given under the auspices of the Regional Fracture Committee of the American College of Surgeons and the Genesee County Medical Society, Hurley Hospital, Flint, Michigan.

contour be taken in consideration, especially in the young, seeming faulty position of bone fragments are still molded into position as in the days antedating the x-ray. It is noteworthy that the attending physician only too often expects the roentgenologist to be the all-round specialist of interpretation, a glorified scientific soothsayer, which, of course, is flattering but leads to a yoke of dependence.

The flat plate herring-bone appearance of acute ileus or the telltale gas bubble in a subphrenic abscess, with the characteristic elevation of the diaphragm admit of no dispute in the diagnosis if taken in conjunction with the history and clinical course. The pathognomonic appearance of pencil-like narrowing in regional ileitis and many other positive findings of the x-ray form the bulwark of the diagnostic aids to the surgeon. Lesions of the large bowel or the stomach need more than ordinary acumen to diagnose unless definite pathologic size has developed. The surgeon expects too much when he looks to the roentgenologist to find the above-mentioned lesions in the initial stages, and negative findings should not deter the surgeon from proceeding with an exploratory operation. It is desirable to be able to localize early stages which do not show gross changes, and careful and minute study, will, in many instances, detect changes in the physiologic contour brought about by the microscopic changes. The contrast obtained by forced gas distention of the bowel lumen has made many early lesions possible of detection. Even the etiological factor can be told within a certain degree of accuracy, due to the predilection of specific pathologic lesions for certain parts of the alimentary tract or bones.

We have to recognize that frequency of x-ray determinations does something to the end of the fractured bones, which retards the formation of callus. X-ray signs of bone dissolution, destruction and regeneration require knowledge of normal anatomy and physiology first, and sequence as well as regional pathology. Early pathologic changes become apparent to the skilled roentgenologist, as an irritable duodenum or pylorus may be recognized before full clinical symptoms of gastric ulcer appear, or an impending Suedeck's syndrome may be prognosticated by the early and persistent atrophy of bone.

To Rowntree and Abel, Cole and Graham, Swick and others, we owe the demonstration of the selective absorption of radio-opaque dyes given orally or intravenously and its use magnificently demonstrated in their widespread application. It is not necessary to remind you of opaque substances introduced through the ureters and per urethra into the bladder and the introduction of an opaque solution into the bladder for determination of bladder malignancies, or as the author lately used it in determination of ruptured urinary bladder.[2] The use of radio-opaque oils or dyes to visualize spinal lesions and vascular pathology has been widely reported, requiring great skill and coöperation of roentgenologist and surgeon. The introduction of gas for ventriculograms also needs the teamwork mentioned above, and the use of ethylene instead of air seems to be gaining favor. The removal of the opaque dyes or oils used is of concern to both roentgenologist and surgeon, and is of great importance to the patient. The surgeon must not forget that microscopic changes do not manifest themselves in an x-ray plate; therefore, osteomyelitis, malignancies, or early bone deposits are not recognized in the early initial stages, and when negative to x-ray must not be dismissed as absent. Localization of foreign bodies on the plate does not always spell a spectacular removal, for I admit many difficulties that I had to cope with, even after excellent x-ray localization.

I can only allude to the brilliant chapter written by roentgenology in the field of therapeutics. especially deep x-ray in pre- and postoperative care of malignancies, as well as the direct attack of the lesion. Many enthusiastic reports in the treatment of acute regional infections have come to the fore, especially in acute postoperative parotitis or thrombophlebitis.

Controlled injection of radio-opaque media into fistulous tracts as well as the visualization of the biliary tract and detection of hidden duct stones by means of the x-ray on the operating table is being put to more frequent use.

The physician and surgeon must educate the laity that a roentgenologist is not a photographer of structures. We know that the x-ray plate is a record of the normal and abnormal anatomy and physiology; its deciphering requires skill and training, requiring a great deal of time and perseverance.

Baetjer and Waters[1] state that the roentgenologist has four inseparable friends, the anatomist, pathologist, internist and surgeon, and I wish to add a fifth one, the physiologist. With them his work rises or falls. The physician and the surgeon should not shed their responsi-

bility and expect the roentgenologist to make the diagnosis for them. The roentgenologist should be considered a highly skilled physician with whom his colleagues coöperate and coördinate as one of the important highways to reach the destination of a workable diagnosis and possible cure, and not the sun around which the medical and surgical diagnosis revolves.

REFERENCES

1. Baetjer and Waters: Injuries and Diseases of the Bones and Joints. New York: Paul B. Hoeber, 1927.
2. Bogart, L. M.: Rupture of the urinary bladder *Amer. Jour. Surg.*, 23: 442, (March) 1934.

DEPARTMENT OF TECHNIQUE

Department Editor: ROBERT B. TAFT, M.D., B.S., M.A., 105 Rutledge Ave. Charleston, S. C.

RESTRAINING DEVICE AND TECHNICAL FACTORS FOR CHEST ROENTGENOGRAPHY OF INFANTS*

By ROGER ALLEN HARVEY, M.D.
ROCHESTER, NEW YORK

CHEST roentgenography in infants requires considerable control over movements of the patient. The variety of restraining devices described in the literature is surprising when one considers that their only purpose is to hold the patient and film in a fixed relation.

FIG. 1. This shows the device in separate parts. Left to right: the cassette holder viewed from the back, the lateral board, the base with uprights, and the seat.

The most common technique is to suspend the patient in front of a vertical or horizontal cassette. The resulting roentgenograms are fairly satisfactory at times, but are difficult to reproduce on the same patient for comparison, and the number of reexaminations is high.

Heilig,[6] Abramson,[2] and Weymuller, Bell and Krahulik[12] have described boards which resemble laboratory animal boards with their multiple restraining straps. Bowen[3] devised a pattern-made cloth garment for wrapping and suspending the smaller infants during the examination. Pancoast and Pendergrass[8] used a modified chair which had a cassette and cloth binder mounted on the back. Wood[14] used a sling with openings for the legs, and restraint was furnished both by a nurse, who held the head and arms, and by a pressure plate held against the lower back. Geissberger[5] and Abraham[1] used seats with leg holes, an upright cassette holder, and a cloth binder. One nurse was required for additional restraint with Geissberger's device, and two nurses with Abraham's. Von Engelmayer[4] and Viethen[10] also used the upright technique with different arrangements for holding the cassette and multiple restraining ties. Kohn and Koiransky[7] used a seat, upright cassette holder with arm holes at the side of the cassette, and no form of restraint. Wimberger[13] used a seat with arm stocks mounted on the sides, and Viethen[11] modified it with numerous arm, leg, and neck restraints. Bowen,[3] in addition to the cloth garment restraint, devised a movable seat and upright cassette holder with a single cloth binder serving as restraint for chest and arms. Simon[9] constructed an elaborate piece of machined equipment which adjusted and restrained practically all of the potentially movable parts of the infant when in the upright position.

The device which is to be described basically resembles several others previously reported. However, it is so modified that it serves efficiently in routine work with all infants from birth to three years of age, and

* From the Department of Radiology of the University of Rochester School of Medicine and Dentistry, Rochester, New York.

in the few cases of older children between three and six years of age where restraint is needed. It has the advantages of combining a means of taking posteroanterior, anteroposterior, lateral, and oblique roentgenograms of the chest, neck, pharynx, and entire spine, and lateral views of the abdomen—all with minimal changes in the position of the patient from one to another of these examinations. Furthermore, it can be constructed of parts of unused equipment common to most departments of radiology, and is therefore an inexpensive device.

The base is a short length of planking measuring 11 by 21 inches. Four inches from one end, uprights measuring 2 by 2 by 22 inches are fastened to the base by screws and angle irons. Seven inches from the top, the uprights are further braced by a connecting band of strap iron. The right hand upright supports a geared roller shaft for winding and tightening a restraining cloth band of the type commonly used with the Potter-Bucky grid. The left hand upright supports the rod which is inserted in the free end of the binder cloth, and also mounts two small blocks on the side for offsetting and holding the bolts of an accessory cassette holder for lateral examinations.

The main cassette holder consists of a bakelite front $11\frac{1}{4}$ by $10\frac{1}{2}$ inches. A welded frame is fastened to the sides and bottom of the bakelite, leaving clearance for cassettes to slide up and down between the bakelite and the frame. Cassettes up to and including those accommodating 10 by 12 inch film fit this slide. Two blocks are mounted on the back of the welded frame so that they fit snugly between the main uprights. These blocks are supported by a connecting band of strap iron in the back which extends beyond them to overlap fully the rear of the main uprights. This gives three surfaces on which the cassette holder slides, namely, the front, inner, and back sides of the uprights. To control this vertical movement of the cassette holder, a thumb-screw is mounted in the iron overlapping the rear of the left upright. This screw can be turned into depressions in a metal plate sunk in the back of the left upright, allowing a 5 inch range of vertical movement.

The seat measures $3\frac{3}{4}$ by 8 inches, is rounded in front, has a short upward projection in back, is padded with cloth, and is covered with oiled silk. It is bolted to a metal cylinder which fits into a cast base. A thumb-screw in this base fixes the seat at any angle on the horizontal plane, and allows 2 inches of controlled vertical movement. The cast base is bolted to a wooden platform 8 by $9\frac{3}{4}$ inches, which slides on a metal track in the main base. Narrow wood strips placed at the sides and ends of the sliding platform area give greater stabilization. The whole seat mount can be secured at any point by turning a winged nut fastened to a bolt extending upward from the base.

Fig. 2. This shows the patient (three months old) in position for a posteroanterior chest examination with attendant steadying the infant's head. Note infant's hands at his sides. A 10 by 12 inch film cassette has been used for illustrative purposes only—in actual procedure a much smaller film would be used on a patient of this age.

An accessory cassette holder for lateral examinations consists of a board 11 by 20 inches. Two iron strips are fastened to the back and extend $1\frac{1}{2}$ inches beyond the edge of the board. They are slotted to fit over bolts extending laterally from the left upright. Winged nuts on these bolts allow rapid tightening of the lateral board. The lower edge of the lateral board is at the same level as the top surface of the main base, and small metal angles fastened to the

FIG. 3. This shows the infant and cassette in position for a lateral roentgenogram of the chest. The patient's hands can be held farther away from the body or alongside of the head, depending on the area of the chest and neck to be examined. A cassette larger than required in actual procedure has been used for illustrative purposes.

lateral board rest upon the main base when in position. A notched block is fastened on the inside of the lateral board and can be raised or lowered by placing its bolts in holes at various levels. For lateral examinations, the cassette is placed on this block and pushed along so that the far edge of the cassette extends past the side of the main cassette holder, past the rod of the binder cloth, and against the small blocks fastened to the side of the left upright. Between lateral examinations, the lateral board is detached and stored.

To prevent sliding of the entire mount, a rubber gripper is fastened under each corner of the main base. The device can be placed on a small mobile table, bench, or roentgenographic table for use.

METHOD OF USE

All clothing is removed from the infant with the exception of the diapers. Occasionally a cotton gown without pins or buttons is allowed. The cassette holder is adjusted to a suitable height and a disposable tissue paper napkin is folded over the front of the bakelite cassette holder. The infant is then lifted to the seat and placed facing the paper-covered cassette holder with his legs and feet projecting under the cassette and between the uprights which are 11 inches apart—thus limiting movement of the legs. Next, the seat is moved forward and locked in position when the abdomen touches the cassette holder, and the upward projection at the rear of the seat is against the lower spine area. The arms are held at the patient's sides, and the cloth binder is tightened until the chest is drawn firmly against the holder. Care in positioning the infant on the seat and in gently tightening the binder so that the chest is square against the bakelite obviates further position corrections. The cassette is placed in the holder, the attendant holds the infant's head so that the chin is directed straight ahead, the tube is centered 6 feet away, and the first exposure is made at full inspiration. The cassette is then replaced by another, and the second exposure is made at full expiration. For anteroposterior directional work, the same procedure is followed except that the patient is placed on the seat in the reverse direction.

For oblique studies, the same cassette holder is used. The cloth binder is loosened slightly to allow withdrawal of one arm (in a left antero-oblique view the right arm is withdrawn, and in a right antero-oblique view the left arm is withdrawn). The seat is loosened, rotated 15 to 45 degrees and fastened with the thumb-bolt. The chest binder is retightened, and the film exposed with the attendant holding the free arm upward and the head straight.

For lateral studies following routine postero-anterior exposures of the chest, the cloth binder is loosened slightly, the arms are withdrawn, and the binder is retightened. The lateral board is slipped in place with the cassette on it. Next the entire device is rotated 90 degrees so that the shoulder away from the film is nearest to the tube. The attendant holds the infant's hands at its back and steadies its head while the exposure is being made. Alternate methods for lateral technique are to place the holding device at right angles either to a vertical Potter-Bucky grid or to a vertical adult chest cassette holder.

Cases of contagious disease are easily man-

aged by placing a clean gown on the infant after it is lifted from bed and by covering both the seat and the front of the cassette holder with disposable tissue paper napkins.

EXPOSURE FACTORS

The exposure chart (Fig. 4) is based on the results of 150 cases between the ages of birth and three years. Of course, factors will vary slightly with different installations and tubes. A distance of 6 feet from cassette to anode is used with all posteroanterior exposures, of 5 feet in oblique exposures, and of 4 feet in lateral exposures. The factors used were 450 milliamperes, 1/40 second exposure, 3 phase rectification, rotating anode tube, Eastman Fine Grain intensification screens, and Blue Brand, Ultra-Speed film. Development is 5 minutes at 65° F. in Eastman Kodalk developer. Other combinations of kilovoltage, milliamperage, and time have been tried but the above factors gave the most satisfactory detail and contrast.

DISCUSSION

The improvement in results following the adoption of various restraining devices has been marked, but in many instances this improvement has been due to greater technical precision rather than to the device itself. Some restraints answer a local problem where chest examinations in infants are carried out infrequently, but these same devices are difficult to adapt to the varied requirements of contagious, acute, and chronic hospital cases and clinic patients of various ages—all coming to the same roentgen department.

Vertical and horizontal positioning each has its advocates, but the essential point seems to be the consistent use of some one method for the most accurate interpretation. Constancy of results with the device described is illustrated in Figure 5. Age is no barrier to vertical positioning because even very young infants are held upright for the regurgitation of air after feeding (Fig. 6). The average time for the patient to be out of his bed for examination on this holder is one and a half minutes. During this interval, two exposures of the chest are

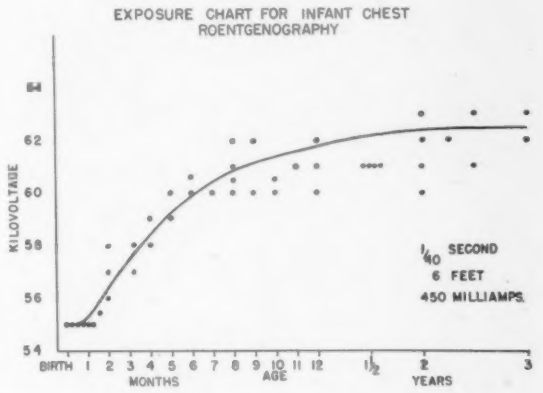

Fig. 4. This chart is compiled from the exposure factors used on 150 cases varying from birth to three years of age. Each dot on the graph represents several cases, and the solid line is an average exposure factor for the various age levels.

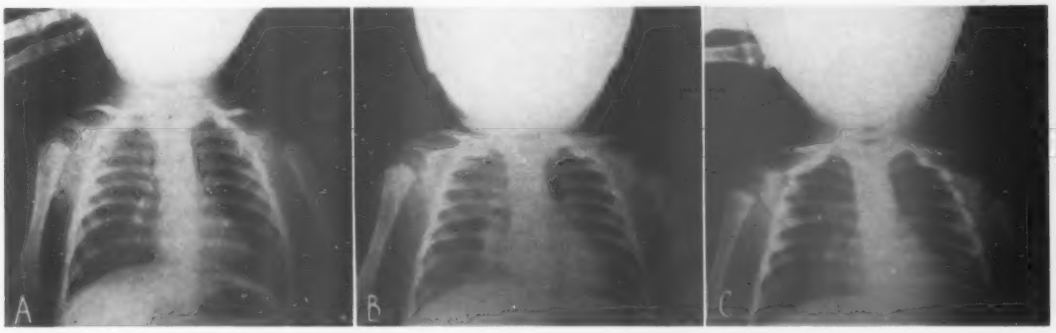

Fig. 5. Showing the constancy of this technique for consecutive examinations of the same patient. *A*, roentgenogram taken February 3, 1941, for suspected right upper lobe pneumonia in a male patient, aged four months. *B*, roentgenogram of the same patient, taken on February 15, 1941. *C*, roentgenogram also of the same patient, taken on March 18, 1941.

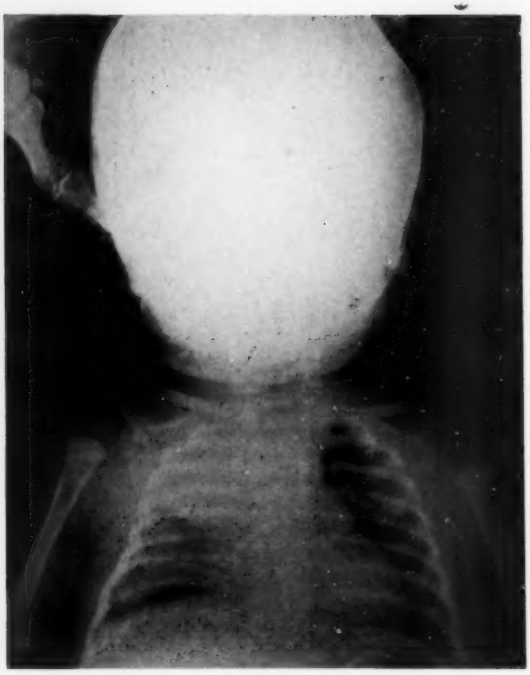

FIG. 6. This patient was born prematurely in the eighth month, developed signs of consolidation in the right upper lung, and was roentgenographed four days after birth.

made. There are occasional cases which cannot be placed upright for chest examination, and only 4 such cases have occurred here in the last 150 infant chest examinations. These 4 cases included 2 in oxygen tents, one in a plaster jacket, and one receiving a hypodermoclysis. In these 4 cases the simple overhead technique was resorted to, and no restraint was necessary because of the condition of the patient.

The most prominent changes noted between films taken in the horizontal and vertical positions are that those taken in the vertical position show greater downward displacement of the diaphragm resulting in a larger lung area exposed to view, a more constant midline relation of the cardiac shadow, and less deformity of the rib cage from external pressure. The upright position with arms at the sides or elbows akimbo introduces no confusing shadows. The scapulae are thrown free of the lung area in as many cases as with the arms held over the head. The apices are free from densities sometimes cast by the folds of muscle and skin when the arms are held close to the sides of the head.

Extra devices for holding the infant's head have been tried here in an attempt to avoid exposure of an attendant to roentgen rays. However, these have been discarded in favor of human support which is more adaptable to the occasional head-banging infant and to the weakness of the very young or ill patient. The problem of exposure of adults to the roentgen rays is not serious because the incidental holding is done by the nurses, students, attendants, or parents who accompany these patients to the department. Repeated exposures to the same person are infrequent because of the rotation of the personnel.

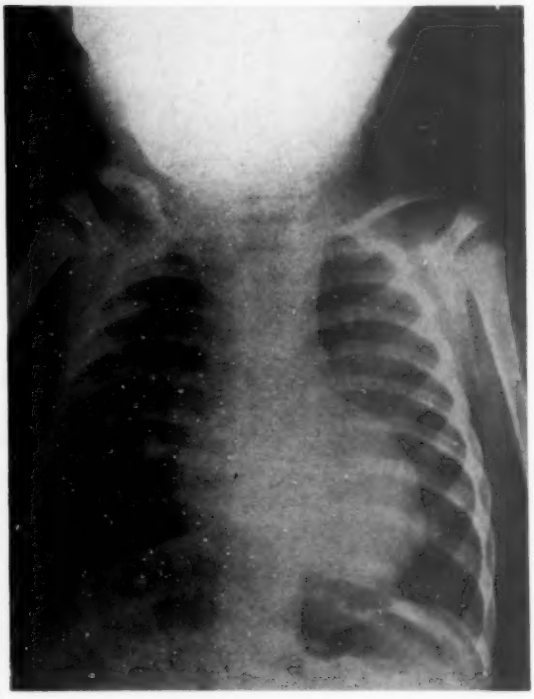

FIG. 7. This patient, male, aged one year, had physical signs and history indicating congenital heart disorder. Three attendants were unable to restrain him in the former prone position for a satisfactory roentgenogram of the chest. This roentgenogram was made from the first attempt with the restraining device, and was taken without other restraint than that afforded by the device.

CONCLUSIONS

1. A device is described for restraining infants during chest roentgenography.

2. An exposure chart based on 150 consecutive posteroanterior chest examinations on infants from birth to three years of age is included.

REFERENCES

1. Abraham, G. Ein Röntgenstühlchen für Säuglingsaufnahmen. *Monatschr. f. Kinderh.*, 1928, *39*, 100–103.
2. Abramson, H. Frames for taking roentgenograms of infants. *J. Am. M. Ass.*, 1928, *91*, 1546.
3. Bowen, D. R. Roentgen examination of the infant thorax; a precision technique. Am. J. Roentgenol. & Rad. Therapy, 1932, *27*, 610–616.
4. von Engelmayer, E. Vereinfachung meines Hängegerätes zur Röntgenuntersuchung von Säuglingen. *Röntgenpraxis*, 1937, *9*, 338.
5. Geissberger, H. A table for use in the radiography of infants' chests. *Radiology*, 1939, *32*, 96–97.
6. Heilig, W. Ueber ein Röntgen-Therapie-Bänkchen für Säuglinge und Kleinkinder. *Ztschr. f. Kinderh.*, 1931, *51*, 263–266.
7. Kohn, J. L., and Koiransky, H. Immobilizing apparatus for taking chest roentgenograms in young children. Am. J. Roentgenol. & Rad. Therapy, 1931, *25*, 100–102.
8. Pancoast, H. K., and Pendergrass, E. P. Roentgenologic diagnosis of diseases of the upper respiratory tract in children. Am. J. Roentgenol. & Rad. Therapy, 1930, *23*, 241–264.
9. Simon, S. Ein neues Hilfsgerät für Röntgenuntersuchungen des Säuglings. *Röntgenpraxis*, 1938, *10*, 485–488.
10. Viethen, A. Röntgenaufnahmegerät für Säuglinge und Kleinkinder. *Röntgenpraxis*, 1934, *6*, 480–481.
11. Viethen, A. Verbessertes Säuglingsstützbänkchen für Durchleuchtungen (nach Wimberger). *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1926, *34*, 554.
12. Weymuller, C. A., Bell, A. L. L., and Krahulik, L. Roentgenographic changes in the thorax of normal new-born babies. *Am. J. Dis. Child.*, 1928, *35*, 837–855.
13. Wimberger, H. Technische Erfahrungen aus der Kinder-röntgenologie. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1922, *29*, 96–99.
14. Wood, H. C., Jr. A frame for holding infants upright during roentgenography. Am. J. Roentgenol. & Rad. Therapy, 1934, *31*, 396–398.

MODIFIED CONTACT ROENTGEN THERAPY CONE*

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THE accessibility of the opening of the cone to lesions in the mouth treated by contact roentgen therapy is an important factor in the treatment of oral cancer. It involves a great deal of adjustment to approximate the opening in the center of the cone to the lesion; and we are not always successful at that. With this in mind a new cone has been devised where the opening is placed more to the side, at the same time allowing sufficient radiation to reach the lesion (Fig. 1).

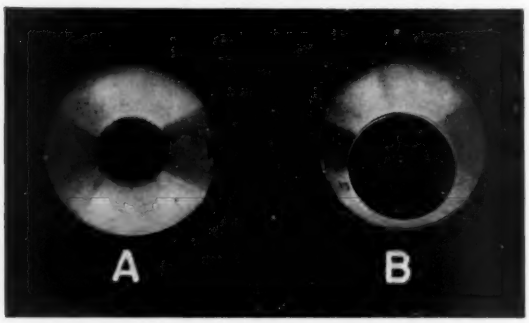

FIG. 1. *A*, the cone usually used with the contact roentgen therapy machine. *B*, the modified cone, showing the eccentric opening, permitting easy accessibility to lesions in the mouth.

The modified cone, although differing from the present one only in the location of the opening, will not only facilitate the proper therapy, but will save the patient a great deal of nervousness while he is being prepared for treatment.

That contact therapy deserves a trial in the treatment of suitable lesions of the buccal cavity is evidenced by the complications so often encountered following the use of deep roentgen therapy on such lesions. The underlying soft tissue is devitalized and is subject to infection and sloughing. The same is true of the underlying mandible that has undergone radiation osteitis, eventually resulting in discharging sinuses, salivary fistula, and necrosis of the whole cheek. Of course, it is true that one cannot attribute this entire destructive process to deep roentgen therapy; but we must equally admit that it is often a contributing factor.

The new cone has been used at the Brooklyn Cancer Institute for a number of months, and we find it very helpful in treating cancer of the mouth.

* From the Brooklyn Cancer Institute, Brooklyn, New York.

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ABSTRACTS OF ROENTGEN AND RADIUM LITERATURE

ROENTGEN DIAGNOSIS

HEAD

Rauch, S., and Krinsky, N. Meningitis caused by Bacterium coli anaerogenes (anaerogenic coliform organism); report of its occurrence in a three week old infant, with temporary cortical insult and recovery. *Am. J. Dis. Child.*, Dec., 1940, *60*, 1386–1404.

Rauch and Krinsky report the case of an infant three weeks old with meninigitis caused by *Bact. coli anaerogenes* (anaerogenic coliform organism), in whom the pneumo-encephalogram and electro-encephalographic studies demonstrated cortical changes. Colisepticemia and bacteriuria also were found. They recommend the use of oral administration of sulfapyridine, blood transfusions and repeated lumbar puncture for patients with this type of meningitis. They also advise caution in relying on the encephalogram alone in formulating a prognosis.

The literature is reviewed with reference to the incidence, pathogenesis, bacteriology, pathology, diagnosis, prognosis and treatment of meningitis caused by "coliform" organisms.—*R. S. Bromer.*

Gowan, L. R., and Masten, Mabel G. Agenesis of the corpus callosum. *Am. J. Dis. Child.*, Dec., 1940, *60*, 1381–1385.

A case is reported of a nineteen months old child, defective from birth, clinically manifesting a marked degree of mental enfeeblement and jacksonian epilepsy. The encephalogram showed the posterior portion of the bodies of the lateral ventricles and the posterior horns to be much enlarged, while the anterior horns were much narrower than usual. The temporal limbs were somewhat dilated. There was an unusually wide separation of the lateral ventricles. Between the lateral ventricles and extending much higher than usual was a dilated third ventricle. There was no air over the convexity of the brain, but air shadows arranged in a radial and dorsoventral direction about the anterior horn were assumed to be on the mesial surface of the hemispheres. The cingulate and callosal sulci were not outlined. The basal cisterns were well filled. The third ventricle could not be visualized in the lateral views. The diagnosis was partial agensis of the corpus callosum.

The authors quote the following dictums (Dyke and Davidoff) as a guide in the encephalographic diagnosis of this condition:

(1) marked separation of the lateral ventricles,

(2) angular dorsal margins of the lateral ventricles,

(3) concave mesial borders of the lateral ventricles,

(4) dilatation of the caudal portions of the lateral ventricles,

(5) elongation of interventricular foramens,

(6) dorsal extension and dilatation of the third ventricle,

(7) radial arrangement of the mesial cerebral sulci around the roof of the third ventricle and their extension through the zone usually occupied by the corpus callosum.—*R. S. Bromer.*

Piquet, Jean. L'exploration radiologique des abcès encéphaliques. (Roentgen examination of brain abscesses.) *Presse méd.*, Dec. 17, 1940, *48*, 1019–1020.

The usual method of roentgen examination of brain abscesses is to remove 2 to 5 cc. pus and immediately afterward inject the same amount of opaque fluid—lipiodol or 20 per cent iodipin. The advantages of roentgen examination are that the opaque fluid penetrates any extensions or diverticula of the abscess and gives important information in regard to the depth of the abscess and consequently in regard to the method of operation. Very large, deep abscesses cannot be simply drained but require extensive resection of brain substance.

The injection of opaque liquid into the brain is not, however, free of danger. The friable walls of the abscess may be broken down and the ventricle infected. The production of iodism and of embolism by the injection of iodipin have also been reported.

The author has a personal method that he thinks obviates the danger. He does not inject the opaque substance immediately after the evacuation of the pus but waits for several days until the formation of connective tissue

strengthens the wall so there is little or no danger of its rupture. Then, instead of injecting the fluid, he inserts into the cavity strips of gauze impregnated with lipiodol. In this way the brain substance that has a tendency to herniate into the abscess cavity is pushed back into its normal place. When the chief cavity has been filled in this way, a little of the contrast solution flows into them and outlines them faintly. In this way the approximate size of a secondary cavity can be determined. Forty-eight hours later when the dressing is changed the secondary cavity can be packed also and its exact boundaries determined. Roentgenograms showing the results of this process are given; also those showing the boundaries of a large brain abscess and those of a cerebellar abscess.

Some writers even claim that the injection of opaque substance furthers cure. The author thinks this is going too far, however. Even roentgen examination is not indicated in all cases, as for example in brain abscesses in children in which the encephalitis quickly fills the cavity and the suppuration stops in a few days. Roentgen examination may also fail in cases in which the secondary cavity is not connected with the first.

He believes that roentgen examination made not less than eight days after removal of the pus by means of packing the cavity with gauze wet with the opaque solution is harmless and may show anatomical details that are valuable in the choice of treatment.—*Audrey G. Morgan.*

ROMANO, JOHN, and MILLER, W. C. Clinical and pneumo-encephalographic studies in presenile dementia. *Radiology*, Aug., 1940, *35*, 131–137.

Both Pick's and Alzheimer's diseases are presenile dementias which show gross and microscopic atrophy of the brain. Pneumo-encephalography is a valuable method of examination, but even with this method it is difficult to make a definite differentiation between the two diseases. The authors present a description of a case of presenile dementia in a woman of sixty-two, illustrated with pneumo-encephalograms which showed symmetrical dilatation of the lateral ventricles and confluent masses of air over the temporal regions and ribbing of the ventricles indicating internal hydrocephalus. The patient's mental state during life had been one of confusion and irritability. As autopsy was not permitted it was impossible to make a definite differentiation between Pick's and Alzheimer's disease.

Flügel published a detailed study of the encephalography and differential diagnosis of Pick's and Alzheimer's disease and said that in the latter there are broad stripes of air over the convexity while in the former there are large confluent masses of air in the frontal and temporal regions. He did not, however, include any encephalograms in the report. The authors' case was probably one of Pick's disease. Pick's disease is said to resemble paresis and Alzheimer's to bear a closer resemblance to senile dementia. A tendency to confabulation is more common in Alzheimer's disease. It did not exist in the authors' case. Convulsions may occur in either disease but they are apt to occur earlier in Alzheimer's disease. Focal neurologic signs occur more frequently in Alzheimer's disease.

It is hoped that this report will lead to a more careful study of pneumo-encephalography in the presenile dementias.—*Audrey G. Morgan.*

GALLETTO, GIACOMO. Studi sperimentali di arteriografia cerebrale. (Experimental study of cerebral arteriography.) *Radiol. med.*, Dec., 1940, *27*, 905–917.

The author gives a brief history of arteriography of the cerebral vessels and describes the technique which he used in his experimental work on the brains of cadavers. He found that the injection of air or water alone is not effective but that a true contrast medium should be used. He found that the best media were thorotrast and umbrathor. When the original thorotrast Heyden was used there was some diffusion of the medium outside the vessels, but when a suitable amount of gum arabic was added it gave very clear arteriograms and the optimum pressure of 150 to 200 mm. could be used without diffusion.

The best arteriograms were obtained by injecting thorotrast under pressure into the internal carotid artery and the vertebral artery of the same side. Direct injection into the lateral ventricles by Dandy's technique did not give any added information. Injection of contrast into the vertebral canal did not have any effect on the cerebral arteriogram except in one case in which it gave an image strictly limited to one side. Probably this was due to the fact that intracranial pressure prevented the filling of the vessels except on the side of the injection.

Injection into the internal carotid and verte-

bral and making the arteriogram in the submento-vertical projection should give a good clear image of the circle of Willis. If it does not it is justifiable to conclude that there is some pathological condition affecting this part of the circulation.

The shadow of the vertebral artery in the section related to the atlas and that of the internal carotid at its point of entrance into the skull where it receives and gives off the posterior and anterior communicating branches produce a characteristic figure 8. This should be remembered in studying arteriograms.—*Audrey G. Morgan.*

Diena, Sergio. Sul comportamento dei tumori secondari osteo-periostali della mandibola nei confronti dell'intima struttura dell'osso colpito. (Relation of secondary osteoperiosteal tumors of the mandible to the intimate structure of the affected bone.) *Arch. di radiol.*, Jan.-Feb., 1940, *16*, 32–35.

The frequent extension by contiguity of malignant tumors of the mouth to the jaw makes it necessary to study all such cases carefully. By means of roentgen examination the earliest changes in the bone can be detected. From a study of such cases the author has found that generally the first development of malignancy in the jaw is between the upper and lower borders of the body of the bone which is made up of spongy substance and does not have the bone tracts that strengthen the rest of the bone. Three cases are described and illustrated. In the first case there was an epithelial ulcer of the floor of the mouth and in the mandible immediately back of the foramen there was an almost circular rarefied zone in which the normal bone structure had disappeared. In the second case the affected zone was larger, involving almost the whole of the body of the bone and had an areolar appearance. The primary lesion was in the labial commissure. In the third case the primary lesion was an ulcerated tumor of the mucosa of the cheek. There was a rarefaction with irregular outlines and with loss of structure in the posterior half of the body of the mandible.—*Audrey G. Morgan.*

NECK AND CHEST

Pilotti, Giuseppe. Mastite nodosa calcificata. (Calcified nodular mastitis.) *Radiol. med.*, Oct., 1940, *27*, 802–803.

A woman of seventy came for examination of the digestive tract. An enlargement of the right breast was noticed which she said had begun in the latter part of her last pregnancy, more than thirty years before. The right breast had become swollen and painful and the secretion of milk had stopped. There had been no redness of the skin, fever or enlargement of the axillary glands. After a few weeks the subjective symptoms had stopped, leaving only enlargement of the breast.

Local examination showed an enlarged breast with the skin over it normal. Hard nodules, which felt like lead bullets, could be felt in the breast. The breast was movable. The left breast showed senile involution. Roentgen examination showed the nodules superimposed on each other; they were of a uniform calcareous opacity.

Acute mastitis, chronic abscess, nodular tuberculous abscess, gummata, etc., could be excluded by the history. The duration of the condition was much too long for it to be tumor and the fact that it was unilateral excluded cyst. Apparently it was a chronic nodular mastitis, which in the course of years had become calcified.—*Audrey G. Morgan.*

Rothman, P. E., and Mapes, R. Massive unilateral pulmonary fibrosis due to obstructive tracheobronchial tuberculosis. *J. Pediat.*, Nov., 1940, *17*, 659–669.

It is generally believed that the commonest cause of extensive unilateral pulmonary fibrosis is tuberculosis. The authors feel that this is not the end-result of an inflammatory process but is due to mechanical bronchial obstruction followed by atelectasis and subsequent fibrosis. This can occur in the primary childhood type of tuberculosis as a result of complete bronchial occlusion from pressure of enlarged mediastinal glands. These cases have a relatively benign clinical course and negative sputa. Bronchial obstruction may also occur in active parenchymal tuberculosis in which tubercle bacilli are present in the sputa. In such cases the obstruction is due to lesions of the bronchial wall from ulcerating glands or direct contact with the bacillus.

The reason for fibrosis occurring in atelectatic lung is not clear. If the obstruction is relieved early fibrosis will not occur. It is well known that atelectasis following massive collapse and continued artificial pneumothorax does not lead to fibrosis. In these cases no nar-

rowing or obliteration of the bronchi occur. A secondary low grade nonspecific infection may explain the fibrosis.

Cases of massive unilateral fibrosis have been frequently described in the literature of adult pulmonary tuberculosis but the condition is a great rarity in children. The authors describe 2 cases and present serial roentgenograms of the chest. They conclude by recommending collapse therapy in massive unilateral pulmonary fibrosis for symptomatic relief in the absence of tracheobronchial ulceration. They feel, however, that this type of therapy may be inadvisable in the presence of such ulceration.—*R. M. Harvey.*

ROVIDA, FRANCESCO. Degli ascessi extrapleurici. (Extrapleural abscesses.) *Radiol. med.*, Oct., 1940, *27*, 768–794.

Extrapleural abscesses are formed between the pleura and the wall of the thorax. The clinical symptoms are generally slight. The patient may have a vague pain at the site of the abscess and a cough. If the abscess is tuberculous in nature the absence of pain is characteristic. There may be an external swelling covered with skin that is edematous but not reddened or fixed. This swelling appears in the intercostal spaces but is not pathognomonic of extrapleural abscess. These abscesses may be divided into two groups depending on their point of origin; they may develop in the soft parts of the wall of the thorax or they may originate from a focus, either tuberculous or septic, in the ribs. Probably the great majority of cases originate from pyemic or tuberculous foci in the ribs.

Diagrammatic sketches are given illustrating the method of propagation of these abscesses and 4 cases are described in detail and illustrated with roentgenograms. The abscesses may be solitary or multiple. The foci in the ribs often do not show, or at least not very clearly, in the roentgenograms. These abscesses show a shadow, the margin of which extends into the transparency of the lung. In the tangential projection the outline extending toward the lung is quite characteristic, making it possible to differentiate it from other conditions, such for example as sacculated parietal empyema. The shadow of extrapleural abscess is longer in its horizontal than in its vertical diameter and the maximum convexity lies opposite the center of the base on which it is implanted. When examination is made in the tangential projection during respiration the outline flattens on inspiration and returns to its original position on expiration. Differential diagnosis from other conditions, such as tumors and gummata, is discussed.

If the ribs are involved treatment should be surgical, no matter whether the infection is pyogenic or tuberculous. If the abscess is tuberculous and in the beginning stage and the ribs are not involved, physical and medical treatment may be tried. Roentgen examination is of value in determining the treatment to be used and in following up the course of the lesion under treatment.—*Audrey G. Morgan.*

COCCO, GIOVANNI. Segni radiologici patognomonici della cisti da echinococco polmonare. (Roentgen signs pathognomonic of echinococcus cysts of the lungs.) *Radiol. med.*, Oct., 1940, *27*, 745–767.

There was a time when almost any round opaque shadow with clearly defined outlines in the lung fields was considered an evidence of echinococcus cyst. This was found not to be pathognomonic, however, as the same appearance was found in other conditions, such as sacculated pleurisy and abscess of the lung.

The author calls attention to a new sign which he considers pathognomonic and reviews the work of the authors who have discussed it before him. The echinococcus in the course of its development causes inflammation of the lung tissue around it and as a result produces a fibrous membrane around the cyst. This adventitial membrane is quite distinct from the true membrane of the parasite and there is always a space between them, even if it is only virtual. The adventitial membrane is made up of changed lung tissue and cannot be detached from the lung. The true cystic membrane is kept stretched and under tension when the cyst is in a perfect condition of vitality but when for any reason pathological conditions occur the membrane weakens and becomes flabby. A suppurated echinococcus cyst of the lung therefore presents two roentgen characteristics: a clear and distinct outline above the gas-liquid level, which is the adventitial membrane, and an irregular wavy upper border of the gas-liquid level, caused by the flabby true cystic membrane floating on its surface.

Four cases of this kind are described and illustrated with roentgenograms.—*Audrey G. Morgan.*

Kirklin, B. R. Lipoid pneumonitis. *Radiology*, Sept., 1940, *35*, 261–267.

In 1920 it was proved that oil introduced by intratracheal injection causes pneumonitis. Since then it has been found that this is a not uncommon condition in human pathology. Five cases of the disease seen at the Mayo Clinic are reported here, one of them confirmed by necropsy. Almost any oil may cause it but perhaps the most common one is liquid petrolatum, because of its common use as a nasal spray and as a laxative. Dysphagia is a common contributory cause.

The disease is generally localized along the basilar and paramediastinal parts of the lower lobes. The process begins in the alveoli where the drops of oil are invaded by phagocytes, resulting in solidification of the oil. The fat-laden phagocytes penetrate the walls of the alveoli and enter the lymph channels. Their accumulation causes tumors which look like paraffinomas. Finally fibrosis occurs. As a result of infection bronchopneumonia may develop.

In uncomplicated cases the symptoms are slight; there is cough, which may or may not be productive and in many cases slight hemoptysis. There is no fever. Râles are likely to be heard, but the physical signs are slight. When bronchopneumonia occurs the symptoms of the secondary disease are apt to overshadow those of the primary disease so that it is not even thought of. But the roentgen picture, even in early uncomplicated cases, shows fleck-like shadows at the base and along the mediastinum. Davis uses the term "miliary mottling" to describe the picture. As the disease advances the bronchi and lymphatic tracts become more pronounced and nodular and finally in severe cases there is fibrosis. Of course the mottling might be mistaken for miliary tuberculosis and one of the important points in diagnosis is that the examiner bear in mind the possibility of this disease. By cooperation between clinician and roentgenologist it should usually be possible to diagnose the disease.—*Audrey G. Morgan.*

Rolland, J., and Tsoutis, N. G. Abcès du poumon consécutif à un méga-oesophage opéré en un seul temps après création de symphyse pleurale artificielle; guérison. (Abscess of the lung following a mega-esophagus operated on in one stage after creation of an artificial pleural symphysis: recovery.) *Presse méd.*, Dec. 17, 1940, *48*, 1024–1025.

A patient was sent to the authors with a diagnosis of abscess of the lung which had been made clinically and confirmed roentgenologically.

Their examination with different incidences —transverse, right and left oblique—which they heartily recommend, showed a chronic suppurated and necrotic pneumonia lying just back of the anterior wall and involving the upper part of the middle lobe near the incisure. But in the posterior mediastinum to the right of the upper dorsal spinal column, there was an abnormal long spindle-shaped clear space bounded by an opaque line about 3 mm. thick; there was a distinct liquid level in it. They considered several diagnoses but one of the physicians they consulted said that it was very evidently a mega-esophagus. This was confirmed by giving the patient a contrast liquid by mouth. The enormous mega-esophagus was probably congenital and had not caused any symptoms.

Probably during sleep food had poured out of the enormous esophagus into the pharynx and been aspirated into the lung, causing a deglutition pneumonia. This is a frequent cause of the lung abscesses seen in America where operations on the tonsils are performed in a routine way that is perhaps a little exaggerated.

The authors injected an irritant liquid by means of a trocar inserted into the fourth intercostal space, which they had chosen for the incision of the abscess. The patient bore the injection without any disturbance except sharp pain for about a minute. It was followed, however, by a myositis of the pectoral muscle, the first case in which this has been seen. As the abscess cavity was not penetrated the muscle must have been infected by the trocar passing through infected parietal lymphatics. The myositis healed promptly and had no other effect than to delay the operation. Generally five days is enough to allow for the consolidation of the pleural symphysis but in this case it was necessary to wait twelve days for operation.

The operation itself consisted of resection of the fourth rib and removal of the intercostal spaces above and below it with the electric bistoury to expose the parietal pleura adherent to the lung. The lung was incised with the electric bistoury and the wall of the abscess destroyed by diathermic coagulation. Recovery was uneventful; the patient was discharged with the wound healed by second intention ten days after the operation without expectoration. —*Audrey G. Morgan.*

DEBRÉ, ROBERT, LAMY, MAURICE, and MARIE, JULIEN. Kystes gazeux congénitaux du poumon et emphysème par obstruction bronchique chez l'enfant. (Congenital gas cysts of the lung and emphysema from bronchial obstruction in children.) *Presse méd.*, Nov. 19, 1940, *48*, 913–917.

Until recent years congenital cysts of the lung were thought to be very rare and incompatible with prolonged life. It is now known that they are not as rare as is generally believed and that they may be tolerated for years. They have been seen in children, adolescents and adults. During this same period emphysema of the lungs from bronchial obstruction has become much better known, thanks to roentgen examination. It is hard to differentiate between these two conditions because both present cavities in the lung filled with gas. For some years the authors have been studying these two conditions in children and now they believe that emphysemas from bronchial obstruction have sometimes been mistaken for congenital cysts, and vice versa.

The first sign of congenital cyst of the lung is often an intense dyspnea. When they do not become manifest until later in life the beginning is less violent. There may be an attack of suffocation and pain in the side, suggesting the symptoms of spontaneous pneumothorax. With very large cysts the physical signs are those of pneumothorax; smaller ones show the signs of cavity.

The roentgenogram of a very large cyst shows an image suggesting that of pneumothorax: the affected side of the thorax is entirely or almost entirely clear; the diaphragm is lowered and flat, the heart and mediastinum are displaced. But there are certain features which indicate cyst; the stump of the hilum cannot be seen even after decompression; the outlines of the cavity, sometimes marked by a fine line, impinge on the diaphragm, heart and borders of the mediastinum. The clear area is never homogeneous; dark lines representing the vessels traverse it. Solitary cysts of moderate size show a rounded regular image bounded by a fine line; they may be opaque for they may be filled with liquid or liquid and air. Multiple cysts show a series of juxtaposed round or oval cavities. No matter what the roentgen picture the best evidence that these are cysts is that they persist unchanged for years. However, the image may be modified by expansion of the cavity, opening of the cyst into a large bronchus or into the pleura, fusion of several cysts or intracystic hemorrhage. After an infection sometimes the image of cyst may disappear and it may require planigraphy to show its wall.

Emphysema from obstruction may be due to foreign body, intrabronchial tumor or pressure of glands from the outside. When the obstruction of a bronchus is complete it causes atelectasis but if the obstructing body forms a valve so that air can enter on inspiration and not be expelled on expiration emphysema is produced. If the obstruction is in a large bronchus it results in lobar emphysema; if in a small bronchus a limited area becomes emphysematous; this is called bullous emphysema. Here, too, the chief symptom is dyspnea and the physical signs are those of pneumothorax.

The roentgenogram shows exaggerated transparency of the affected lobe, increased surface of the lobe, lowering and partial fixation of the diaphragm on the affected side and exaggerated excursion on the other side. The heart and mediastinum are drawn to the normal side on expiration and sometimes there is a pendulum movement of the heart which is drawn to the diseased side during inspiration. The roentgenogram may also show the body that is causing the obstruction.

There are two things that are of importance in differentiation between these two conditions: first the demonstration of the body causing the obstruction in emphysema and second the appearance of an image in tissue that has been normal previously; this argues against congenital cyst. Disappearance of the image also argues in favor of emphysema. The differentiation may be easy, difficult or practically impossible, depending on the case.—*Audrey G. Morgan.*

POPPI, ARRIGO. Valutazione di alcune misure ortocardiografiche e dei metodi cardiovolumetrici nel vivente, in base ai risultati di uno studio di biometria del cuore nel cadavere. (Evaluation of some orthocardiographic measurements and cardiovolumetric methods in living subjects, based on the results of a biometric study of the heart in the cadaver.) *Radiol. med.*, Dec., 1940, *27*, 918–932.

The author has previously made a study of the biometry of the normal heart in cadavers and has published the results in a series of articles in *Arch. di patol. e clin. med.*, for 1939 and 1940. He now makes a comparison of these measurements and those obtained by studying

normal living subjects with the measurements obtained on orthodiagraphic examination.

He uses the abbreviation DLo for the length of the heart, DLa for the width and DApO for its depth on the orthodiagram. The DLo and DLa correspond very well to the anatomical measurements but the DLa is on the average smaller than it is in reality. Tables are given showing the relationship of the various measurements to each other and to various physical norms, such as height, weight, diameters of the thorax, height of the sternum, etc. The anatomical variability of the three measurements corresponds to their orthodiagraphic variability.

There is correspondence between the cord of the left inferior arc of the orthodiagram and the cord of the left ventricle in the isolated heart. This measurement should not be neglected for the author has found that it is closely correlated to the capacity and the weight of the heart. It seems that the most accurate orthodiagraphic method for obtaining an index of the heart which shows the real size of the organ is that proposed by Benedetti and Bollini: the volume of the heart = DLo × DLa × DApO × 0.45. The correlations between the heart and the general bodily measurements, as close in the living subject as in the cadaver, are those: (1) between the weight of the body and the diameters and the volume of the heart; (2) between the transverse diameter of the thorax and the diameters DLo and DLa; (3) between the total volume of the abdomen, determined by Viola's method and the volume of the heart; (4) between the volume of the trunk, calculated by Viola's method and the volume of the heart.

In the cadaver there is a very close correlation between the average circumferences of the arms, the forearms, the thigh and the calf and the weight, volume and diameters of the heart. This is certainly a manifestation of the relationship existing between the general muscular development of the body and the size of the heart. It would seem to be worth while to make a study of these correlations in the living subject also and the author, in collaboration with Dr. Marzocchi, is making such a study.—*Audrey G. Morgan.*

Cardillo, Furio. Diverticoli funzionali dell'esofago. (Functional diverticula of the esophagus.) *Radiol. med.*, Nov., 1940, *27*, 880–882.

Functional diverticula of the esophagus are visible only on contraction of the musculature and disappear on relaxation. A typical case is described in a man of fifty-two and another more complex in a woman of seventy-seven who had complained for six years of progressively increasing difficulty in swallowing. Roentgen examination showed the upper half of the esophagus dilated, particularly its middle part, reaching a maximum diameter of about 7 cm., and becoming constricted a little below the sac where there was a diverticulum the size of a large hazelnut. Below this the diameter of the esophagus was normal down to the opening into the stomach, where the opaque medium stopped.

The patient grew worse and died. Autopsy showed the facts above described. Histopathological examination of the wall showed many areas in which the mucosa had the same structure as that of the stomach. In this case pulsion diverticulum coexisted with idiopathic dilatation of the esophagus. It seems to support the hypothesis that some pulsion diverticula are final stages of functional diverticula. On the other hand, the existence of a dilatation of the esophagus without hypertrophy of the musculature of the cardia would suggest a disturbance of innervation or a malformation. The latter theory is supported by the presence of tracts of gastric mucosa along the middle and lower part of the wall of the esophagus. This is quite frequent at the cardia and in the lower part of the esophagus but exceptional in the middle part.

The relations between disturbances of innervation, malformations and dilatations of the esophagus are by no means clear.—*Audrey G. Morgan.*

ABDOMEN

Burdick, W. F. Peptic ulcer in children; report of ten cases. *J. Pediat.*, Nov., 1940, *17*, 654–658.

This article emphasizes the fact that the signs and symptoms of peptic ulcer in children are not typical. Although peptic ulcer is not common in children it does occur. The diagnosis can only be made, as a rule, by roentgenographic examination. The typical defect is difficult to demonstrate on films in children and we must depend mainly on roentgenoscopic examination. The author reports 8 cases occurring in a series of over 21,000 admissions in a children's hospital. Two additional cases are added from his private practice. A diagnosis of ulcer was made in 7 roentgenoscopic examinations, 2 were

diagnosed by postmortem examination, and the diagnosis in the final case was made on the history of rather typical hunger pain with food relief, hematemesis and melena. The article is concluded with a plea for more frequent use of the roentgen ray in children with indefinite gastrointestinal complaints in order to avert complications such as hemorrhage or perforation.—*R. M. Harvey.*

AGATI, DINO. Quadri radiologici di invaginazione gastro-gastrica e gastro-duodenale. (Roentgen pictures of gastrogastric and gastroduodenal invagination.) *Radiol. med.*, Nov., 1940, *27*, 865–875.

The author describes 3 cases, 2 of gastrogastric and 1 of gastroduodenal invagination. They are illustrated with roentgenograms. These cases are quite unusual. Five are reviewed from the literature. Ascending gastrogastric invagination is more frequent than the descending form. In the author's first case the invagination was caused by an ulcer, the niche of which could be seen in the roentgenogram. The usual picture is that of a hook-shaped shadow, concave distally in the ascending variety and concave proximally in the descending variety. In the second case described there were two hook-shaped images, one at the lower boundary of the body opening distally and the other at the upper boundary of the antrum opening proximally. Operation showed a case of ascending gastrogastric invagination caused by tumor. The third case was one of invagination of the pyloric part of the stomach into the duodenum brought about by juxta-pyloric polypous gastritis.

The diagnosis in these cases is only one of probability. In the first and third cases there was no surgical confirmation. In the second case operation showed a brief capping of the body of the stomach over the antrum but it could hardly be called a true invagination. Similar pictures may be caused by hypertonia, hyperkinesia, spasm, segmental atony, annular peristalsis, etc.—*Audrey G. Morgan.*

BRONAUGH, W., and LATTIMER, R. D. Intestinal obstruction from inspissated meconium. *Am. J. Dis. Child.*, Dec., 1940, *60*, 1371–1374.

Several cases of intestinal obstruction in the newborn due to meconium have been reported. Some writers have termed the condition "meconium ileus," a name which Bronaugh and Lattimer think is particularly appropriate, as undoubtedly ileus is present at some time in every case and the cause is inspissated meconium. Thirty-six hours after the birth of their patient, he was regurgitating everything taken by mouth and an oil enema was ineffectual. The abdomen was tense and tympanitic and no peristalsis could be detected. A mass the size of a dill pickle and of a somewhat similar shape could be palpated in the right side of the abdomen. A survey roentgenogram demonstrated much gas in the bowel. A barium sulphate enema showed a collapsed colon and the cecum lay in the upper right quadrant of the abdomen. No barium passed into the ileum. At operation an obstruction due to thick, gummy and wax-like meconium was found and was relieved. Recovery was, however, precluded by the congenital anomaly which was present, an absence or fibrosis of the terminal portion of the duct system of the pancreas, with obstruction and atrophy of the pancreatic tissue and resultant failure of pancreatic secretion.—*R. S. Bromer.*

PORTA, REMO. Diverticolo della regione pilorica. (Diverticulum of the pyloric region.) *Radiol. med.*, Nov., 1940, *27*, 877–878.

The author has never before seen a case of diverticulum of the pyloric region and has never seen one described in the roentgenologic literature with the possible exception of one by Ratti in which a diverticulum of the bulb of the duodenum might have been interpreted as being in the pylorus.

This case was in a man of thirty-nine who for four or five months had had periodic attacks of gastralgia with foamy, acid vomitus. The attacks lasted for a few days and then passed off completely. He was examined two weeks after one of these attacks when he felt perfectly well.

Roentgen examination showed a round extroflexion near the end of the pylorus the size of a cherry, extending latero-posteriorly; its outlines were very distinct. The pyloric canal was slightly dilated. The diverticulum was connected with the terminal part of the pylorus by a narrow peduncle 1–2 cm. long. Both in the diverticulum and the peduncle the folds of the mucosa could be seen. They were very much hypertrophied. No peristaltic contractions could be seen in the diverticulum. The bulb and second part of the duodenum were normal. The stomach emptied in normal time and there was no residue of barium in the diverticulum.

The author believes this was a congenital diverticulum and probably a complete one. The

absence of contraction of the walls of the diverticulum may have been due to the marked atrophy of the muscular layer; the regularity of the margins of the diverticulum seems to exclude ulcer.

The patient's attacks of pain were probably caused by inflammation of the mucosa due to stagnation of acid gastric juice in the diverticulum. At the time of the examination there was no stagnation of contrast medium in the diverticulum; the patient was well at the time.—*Audrey G. Morgan.*

Gregori, Angelo. Documentazione radiologica di fistola gastrocolica. (Roentgen demonstration of gastrocolic fistula.) *Radiol. med.*, Oct., 1940, *27*, 795–802.

Often diarrhea after meals, emaciation and periumbilical pain are the only clinical symptoms of gastrocolic fistula. Pain, when it is present, may not be confined to the fistulous tract, but may be generalized over the whole abdomen and the emaciation of course only comes on gradually. So it may be impossible to diagnose the condition clinically and the only means of diagnosis is roentgen examination.

A case is described and illustrated. The patient was a man of sixty. For about two months he had had diarrhea, periumbilical pain and was losing weight. A barium meal was given which passed rapidly through the stomach and into the transverse colon. A funnel-shaped fistulous tract was seen connecting the two organs. In addition to the direct sign of visibility of the tract there were the indirect signs of rapid emptying of the stomach and the fact that the transverse colon became visible at once and the small intestine did not fill until later.

There has been a difference of opinion in these cases as to whether examination should be made by means of a meal by mouth or by an opaque enema. The author thinks the opaque meal is best, using the enema only as a supplementary method of examination.

The fistula in this case was at about the middle of the greater curvature. The canal was fixed and rigid, as were the viscera surrounding it, indicating that the lesion was probably a malignant growth with a crateriform fistulization into the transverse colon. In some such cases there is a reflux of gas from the colon into the stomach, or Bocchi's sign and even more rarely Jansson's sign is seen, or relative stenosis of the second half of the transverse colon.—*Audrey G. Morgan.*

Salvadori-Paleotti, Giorgio. Grossa cistifellea simulante una cisti calcificata. (Large gallbladder simulating a calcified cyst.) *Radiol. med.*, Dec., 1940, *27*, 948–949.

The roentgenograms from a woman sixty-seven years of age are reproduced. For twenty years she had been subject to attacks of hepatic colic; recently they had become worse and she was in poor general condition. The attending physician could feel a swelling extending below the right costal margin, though the patient's abdominal wall was very fat.

The first roentgenogram showed a large, ovoid, calcified mass which suggested a calcified cyst. In a later roentgenogram there was a round, opaque shadow which from its site and size was thought to be an opacified gallbladder, particularly as it disappeared on a later examination. An annular shadow at the lower pole of the calcified mass suggested calculus, though it was possible that it was a daughter cyst.

Operation a few days later showed an enormous calcified gallbladder full of calculi and bile, with the common duct greatly dilated and opacified.—*Audrey G. Morgan.*

GENITOURINARY SYSTEM

Sorrell, L. E. Roentgen visualization of some of the commoner lesions of the lower genitourinary tract. *Radiology*, Sept., 1940, *35*, 341–345.

The author describes 9 cases of lesions of the lower genitourinary tract diagnosed by intravenous pyelography or the injection of opaque medium or air into the bladder without cystoscopic examination. They were cases of dermoid tumor, seminal vesiculitis, diverticulum of the urethra, prostatic calculi, enlarged prostate, bladder diverticulum, bladder calculus, carcinoma of the bladder and bilateral ureteral regurgitation. He emphasizes the value of these modern methods of diagnosis.—*Audrey G. Morgan.*

Shiflett, E. L., and Keith, D. Y. The clinical application of urinary dynamics. *Radiology*, Sept., 1940, *35*, 336–340.

The authors discuss urinary peristalsis as a dynamic function of the urinary tract and urge a closer study of it by means of intravenous urography as a means of settling many disputed questions in urinary pathology. They discuss the urographic findings in obstruction in the urinary tract and in ptosis. In the latter condi-

tion they urge making a urogram first in the supine position and then in the standing position and describe a case in which there was no evidence of abnormality of filtration or excretion with the patient lying down but when the patient stood erect the kidney dropped and there was considerable rotation on its longitudinal and vertical axes.

They do not claim that a sharp differentiation can always be made between different degrees of acute obstruction but an attempt to make such differentiation promotes keen observation and clear thinking. These phenomena cannot be produced at will in experimental animals and so it is necessary to study them by making urinary function visible in the human subject by means of intravenous urography.—*Audrey G. Morgan.*

ARENDT, J., and MASLOW, L. A. Blocking of the ureters in intravenous pyelography by means of filling the bladder with oil. *Radiology*, Sept., 1940, *35*, 350–352.

The main causes of misinterpretation of the pyelogram in intravenous pyelography are incomplete filling of the pelves and spasm of the pelvis and ureter. An attempt is generally made to avoid these defects by pressure of the ureters against the spine or upper sacrum. This pressure may, however, cause further spasm or it may displace or distort the ureter. But the necessity for compression may be avoided by filling the bladder with from 150 to 200 cc. of oil. This keeps the dye back in the ureters and pelves. The author uses mineral oil which is definitely harmless. This gives a more complete filling of the pelves and calyces and causes less spastic and reflex contraction than other methods. It gives a clear outline of the lower pelvic portion of the ureters which is usually obscured by the dye in the bladder. The method is harmless when properly used. It is contraindicated in cases in which catheterization of the bladder would be contraindicated, particularly in severe urethritis, severe infections of the bladder and in old prostatics with chronic residual urine. Oil embolism is possible theoretically. Therefore the method should not be used in advanced lesions of the bladder or of hemorrhage from the bladder. The oil should not be injected under too high pressure.—*Audrey G. Morgan.*

GIORDANO, GIOVANNI, Insolito reperto radiologico di calcolosi renale. (Unusual roentgen finding of renal calculi.) *Radiol. med.*, Oct., 1940, *27*, 804–805.

A woman of twenty-four had been delivered eight days before she came for examination because of increase of lumbar pain which she had had during the latter part of pregnancy. The pain had been attributed to a slight cystitis. After delivery, in addition to the increased pain, micturition had become painful, fever had developed and she showed meteorism and a dark red skin eruption.

Roentgen examination with the patient lying down showed many opaque spots of various sizes and shapes, some rounded, some facetted, all over the right flank. The upper ones were above the 11th rib, the lower ones a finger's breadth from the crest of the ilium and some median ones were superimposed on the shadows of the lumbar vertebrae. A lateral projection showed two of the shadows projected onto the spinal column while the rest were anterior; the shadows changed position when the patient was moved.

The diagnosis made was "multiple calculi, most of them mobile, probably located in a large hydronephrotic kidney with many chambers," though it was thought possible the calculi might be in an enormously enlarged gallbladder. Ascending pyelography confirmed the diagnosis of stones in a greatly enlarged hydronephrotic kidney divided into various sacs of different shapes and sizes with delicate septa between them. The kidney tissue was completely destroyed except for some small islands at the upper pole on the posterior surface. A roentgen examination a few days later did not show any calculi in the gallbladder. This is an unusual case and brings up the question of how the pregnancy could have progressed with such a diseased and enlarged kidney.—*Audrey G. Morgan.*

GALLAVRESI, LUIGI. Quadri radiologici di complicazioni a carico delle vie urinarie superiori, conseguenti a cancro dell'utero. (Roentgen pictures of complications in the upper urinary tract resulting from cancer of the uterus.) *Radiol. med.*, Nov., 1940, *27*, 843–856.

In a large percentage of cases of cancer of the uterus there are complications in the upper urinary tract. There may be inflammation, compression or deformation of the bladder but perhaps the most frequent and serious complication is stenosis of the terminal part of the ureter that runs through the broad ligament. These stenoses are generally caused by propagation of the tumor to the parametrium. The

stenosis of the ureter may assume different forms and vary in extent, depending on the nature and extent of the infiltration of the parametrium. Finally, however, it leads to stagnation of urine, resulting in hydronephrosis. Roentgenograms are given showing various types and degrees of ureteral stenosis.

The severity of the stenosis and consequent hydronephrosis do not run parallel with the seriousness of the tumor or the extent of infiltration of the parametrium. It is the direction taken by the infiltration rather than its volume that determines the degree of stenosis. In very large tumors with extensive infiltration the ureter may not be compressed at all, but merely displaced. In many cases the displacement consists of a straightening of the pelvic curve of the ureter.

The clinical symptoms are not very characteristic. The first symptom is attacks of pain which may be dull or acute and may be localized at the site of the compression or radiate in different directions. Gradually signs of hydronephrosis develop. The course may be aseptic until the hydronephrosis has reached a very advanced stage. If infection takes place signs of inflammation appear. When the hydronephrosis is very advanced, especially if it is bilateral, signs of insufficiency of the kidney—uremia and anuria—develop and cause the death of the patient. This is the most frequent termination in cancer of the uterus.—*Audrey G. Morgan.*

Kretschmer, Herman L. Adenomyosarcoma of the kidney (Wilms tumor). *Arch. Surg.*, Aug., 1940, *41*, 370–384.

The pathogenesis of Wilms' tumor is discussed by the author but no definite conclusions are presented. The author then reports in detail 3 cases of large adenomyosarcoma in young children. In all of these, the tumors were resistant to radiation doses of 2, 436 r, 3,192 r and 2,000 r respectively. All 3 patients died within one year after the diagnosis was made.

Retrograde pyelograms were more successful in demonstrating the deformity of the kidney than excretory pyelograms. In one patient, films of the chest showed no metastases but autopsy soon after showed the lungs were riddled with metastases.

The author is of the opinion that preoperative irradiation followed by nephrectomy and postoperative irradiation are the therapeutic procedures to be followed even though the outcome by any method of treatment is generally fatal.—*G. W. Chamberlin.*

Elward, Joseph F., and Spire, R. Lee. Bilateral hypernephroma. *Radiology*, Sept., 1940, *35*, 274–281.

Hypernephroma is a tumor of the kidney assumed to originate from suprarenal tissue, but recently the suggestion has been made to call all kidney tumors nephromas. The classical triad of symptoms of this form of tumor is hematuria, pain and palpable tumor of the kidney. But these may not be present in early malignancy or the encapsulated benign type frequently seen at autopsy. In that case diagnosis must be made by roentgen examination either by roentgenography of the kidneys, pyelography, pneumoperitoneum, pneumoroentgenography or examination of the colon and stomach for displacement.

Bilateral hypernephroma is extremely rare. The authors have found only 4 cases described in the literature, abstracts of which are given. they add a case of their own which was very unusual in that the symptoms were not from the kidney but in the mediastinum. The patient, a salesman, aged thirty-six, came for examination February 12, 1935, on account of a feeling of fullness in the neck when he leaned forward. Examination showed a mediastinal new-growth thought to be lymphosarcoma. The tumor was at first radiosensitive but recurred and was then resistant to further irradiation. The patient died December 8, 1935, of hypostatic congestion and edema of the lungs. Autopsy showed extensive bilateral hypernephroma of the kidneys and surrounding tissues with multiple metastases and extensive involvement of the mediastinum. The patient had had no genitourinary symptoms during life. It is possible that the tumor developed primarily in a so-called renal rest in the mediastinum and that the kidney tumors were metastases.—*Audrey G. Morgan.*

Harrison, J. Hartwell. Trauma to the kidney. *Surg., Gynec. & Obst.*, Jan., 1940, *70*, 93–104.

Trauma to the kidney may result in (1) contusion without rupture of the confining membrane of the kidney, (2) contusion with extravasation of blood into the renal fossa, (3) contusion with laceration extending into the renal pelvis, (4) complete rupture.

The cardinal sign of severe renal trauma is

hematuria. Other diagnostic data depend upon the correlation of the history, repeated physical examinations, urinalysis, daily measurement of the fluid exchange, studies of the blood, roentgenographic examinations and cystoscopy. When excretory urography is employed as a diagnostic procedure it should be delayed for at least twelve to twenty-four hours after the acute injury because of a tendency for gaseous distention of the intestine to obscure the detail and also because of the impaired renal function which occurs immediately after the injury. Satisfactory urograms can be obtained showing the nature and extent of the lesion if sufficient time has elapsed so that renal function is adequate. The value of this examination, in addition to demonstrating the anatomical deformity of the kidney due to injury, is also demonstrated in those cases in which there is some congenital or acquired lesion of the kidney which has antedated the trauma.

Conservative treatment, in many instances of acute injury to the kidney, yields good results. The damaged kidney has a remarkable ability to return to normal function and relatively normal anatomy. The absolute indications for operation are persistent hemorrhage, urinary extravasation, or renal infection.—*G. W. Chamberlin.*

ROENTGEN AND RADIUM THERAPY

LAWRENCE, JOHN H. Nuclear physics and therapy: preliminary report on a new method for the treatment of leukemia and polycythemia. *Radiology*, July, 1940, *35*, 51–60.

Radioactive isotopes of almost all of the chemical elements can now be produced. These radioactive isotopes have the same chemical characteristics as the inactive elements, but they also give off rays similar to those emitted by radium. When the radioactive elements are given to an animal orally or by injection they behave chemically like the non-active element, but if given in large amounts they produce actions similar to those of radium or roentgen rays. Their half-lives are much shorter than that of radium. The activity of radium is reduced to half at the end of 1,550 years but these elements are reduced to half their original activity in a matter of a few days to a few weeks.

One of the uses of the radioactive isotopes is as tracers. Any given radioactive element gives off a certain number of radiations and by counting the radiations emitted by a given tissue it is possible to determine the element contained in it. In this way iron or other elements given for therapeutic purposes can be traced through the body. It is hoped that in time a suitable radioactive element can be incorporated into some compound that can be localized in tumor tissue so that the tumor can be treated without injuring the surrounding tissues.

Studies of leukemia have shown that leukemic tissue has a greater uptake and exchange of phosphorus than normal tissue. As leukemic tissue, bone and bone marrow take up a relatively high concentration of phosphorus and as beta rays are emitted by radiophosphorus it seemed probable that radiophosphorus might prove of value in the treatment of leukemia.

The author has been using this method of treatment for the past two years in chronic myelogenous and chronic lymphatic leukemia. Five cases of chronic leukemia and 2 of polycythemia vera treated in this way are described. The results were good in all of them. Of course it will require more work on a large number of patients over a period of years before this method of treatment can be properly evaluated.—*Audrey G. Morgan.*

MADRAZO, MANUEL F. Brief observation on the erythrocyte sedimentation in relation to irradiated malignant tumors. *Radiology*, June, 1940, *34*, 668–670.

The factors that influence sedimentation of the erythrocytes are discussed. The test is not specific and therefore cannot be used in diagnosis but it seems to have some value in prognosis in some diseases. It has been recommended for differentiating benign from malignant tumors. It is generally agreed that an increased sedimentation rate means cancer.

The author suggests a study of the sedimentation rate following irradiation of tumors. He has irradiated guinea pigs and found that irradiation always causes an increase in the rate of sedimentation. He has also found it increased in women irradiated for uterine fibromas.

He has not studied enough cases to permit of his giving statistics or reaching conclusions. He wrote this paper simply to stimulate an interest in the subject among roentgenologists. He proposes that studies be carried out in different countries and their results compared at the next International Congress so that the observations may be confirmed or corrected.—*Audrey G. Morgan.*

Popp, Walter C., and Watkins, Charles H. The hematologic diagnosis and roentgenologic treatment of myelogenous leukemia. *Radiology*, June, 1940, *34*, 663–667.

Myelogenous leukemia is divided into four stages—the acute, subacute, chronic and aleukemic—and the clinical symptoms and blood picture in each stage described.

Roentgen treatment is contraindicated in the acute stage, and in the aleukemic stage it must be given very cautiously. It gives the best results in the chronic stage. The author gives small doses over nine spleen fields, so arranged that the whole spleen is covered. In this way as many as nine treatments can be given without irradiating the same skin area twice. In subacute myelogenous leukemia the dose should not be more than 75 to 80 r, measured in air. In the chronic form as much as 225 r per field may be given. Daily treatments are given as long as the count does not decrease rapidly. When the desired level is reached the treatment should be stopped until the count shows a marked tendency to rise again. The count should not be brought down to normal because it continues to decrease for some time after treatment is stopped. If it is originally 75,000 it can safely be reduced to 20,000 to 25,000; if it was 150,000 it can be reduced to 50,000 to 75,000. In the aleukemic form not more than 75 r should be given per day and small fields should be used.

After treatment in any form of myelogenous leukemia a monthly blood count should be made; when there is a tendency to progressive increase treatment should be resumed. The disease can be controlled better and for a longer period in this way than in any other. The follow-up method is almost as important as the treatment. Roentgen treatment is better than any other method as a palliative treatment.

Three things should be avoided in these cases: first, the habit some roentgenologists have of giving a "little bit" of treatment without knowing just how much it is or following up the blood picture carefully; second, irradiating the long bones, for this seems to hasten the course of the disease; third, the use of 200 kilovolts. The authors use about 135 kv., and their experience is based on 350 cases. The 200 kv. irradiation may produce more rapid immediate results but the patients become refractory much sooner than with the treatment described above.—*Audrey G. Morgan.*

Mattick, Walter L. The diagnosis and treatment of cancer of the tonsil. *Radiology*, Sept., 1940, *35*, 268–273.

The author reports 162 cases from the State Institute for the Study of Malignant Diseases, Buffalo, N. Y. Primary healing was seen in 36 of 57 cases, or 63.5 per cent, from 1929 to 1935. Local recurrence developed in 23 of these, or 63.8 per cent.

The great majority of these cases, 91 per cent, are in males and approximately two-thirds of the cases occur in the fifth and sixth decades of life. The patients generally complain of sore throat and pain in the region of the tonsil on swallowing. Inspection of the fauces should be supplemented by palpation with the gloved finger, which will often show induration. This is one of the earliest signs of the disease. If there is unilateral hypertrophy with no ulceration or induration it is apt to be lymphosarcoma rather than the commoner form of squamous cell epithelioma. If there are enlarged lymph nodes in the neck a careful search should be made for a primary tumor in the upper respiratory tract. Enlargement of the nodes at the angle of the jaw is one of the most unfavorable signs in prognosis. A biopsy may be made and the specimen examined if treatment can be given promptly afterward.

Surgery has not proved successful in the treatment of cancer of the tonsil. The best treatment is external irradiation over a field covering the involved area and the first line of nodes. The treatment is given with 200 kv. roentgen rays of 0.16 Å λ eff. or shorter wave length, including teleradium pack if available, continued for twenty to thirty days according to Coutard's method. After the reaction has subsided radon gold seeds of not more than 1 mc. each are implanted under local anesthesia. Careful mouth hygiene should be used during the treatment. If enlarged glands persist after the treatment they may be excised and radon seeds implanted in the bed. If this fails to cause regression of the nodes a radical neck dissection may be performed in young patients who have a good chance of three or more years' survival.

Since improved methods of irradiation have been adopted three year arrests may be expected in 35 to 40 per cent of early cases and in 19 per cent of the cases with involvement of the neck glands.

In the discussion Dr. Eley approved of Dr. Mattick's method of treatment and said that

in non-ulcerated cases biopsies should be taken with great caution and preferably after irradiation, as some of the lesions may be lymphosarcoma. In selected cases a portal through the open mouth obtained by the use of a special metal cone or cylinder may be used when the jaws can be separated far enough. In using the radon seeds care should be exercised in estimating the dosage and spacing the implants and the greatest possible care for asepsis should be used during the implantation. Metastases in the cervical lymph nodes are often more radioresistant than the primary lesion and in such cases the nodes may be exposed by incision so that the seeds can be implanted under direct vision and palpation.—*Audrey G. Morgan.*

GRYNKRAUT, B. De la radiosensibilité des tumeurs malignes. (Radiosensitiveness of malignant tumors.) *Presse méd.*, Nov. 13–16, 1940, *48*, 899–900.

It has been found that the lethal dose of radiation for tissue cultures is 25,000 r, while that for living rats is 1,080 r and for living guinea pigs 1,500 r; that is to say, the living body is much more radiosensitive than tissue cultures. This is probably due to the presence of sensitizing substances in the living body which change the light and make it more assimilable by the tissues.

To study the effect of irradiation on the body of the rat and on tumor tissue experiments were performed on rats. The animals were given a fatal dose of radiation which killed them in a few days. This dose did not kill the tumors (Jensen sarcoma) on the bodies of the animals by direct action of the rays, for when such tumors were inoculated into other rats an hour after the irradiation they took. But when they were inoculated into fresh animals two, forty-eight, and seventy-two hours after the irradiation of the original animal the weight of the tumors was progressively less as the time increased; that is the vitality of the tumors was decreased by remaining on the body of the irradiated rat. This is called the time factor.

There is also a space factor in irradiation; that is, a large surface will stand only a small amount of irradiation while a small surface can stand a much larger dose. This is because the large surface contains more sensitizers. Irradiation through a grill enables a larger surface to be irradiated.—*Audrey G. Morgan.*

RABB, W. Roentgen treatment of the adrenal glands in angina pectoris. *Ann. Int. Med.*, Oct., 1940, *14*, 688–710.

The therapeutic effect of roentgen irradiation of the suprarenal glands was studied over a period of two and a half years on 100 patients with angina pectoris. Eighty-five of the patients were males. All gave the typical story of angina pectoris and 53 had a stenocardiac pain at rest as well as on exertion.

Treatments were given three times on each side of the midline over the adrenal area. Factors: 200 to 250 r, 0.5 mm. Cu plus 1 mm. Al, 180 kv., 4 ma., size of fields 10×15 cm.

The basis for a trial of radiation therapy is the theory that angina pectoris is due to an acute anoxemia of the heart muscle which is caused by the specific effect of sudden discharges of adrenalin from the suprarenal glands; increase of myocardial oxygen consumption without adequate dilatation of the sclerotic coronary arteries.

The effects of treatment were based on the patient's own statements and, in 38 cases, electrocardiograms also.

Forty per cent of the cases had a complete or nearly complete disappearance of their symptoms for a minimum of three months and a maximum of twenty-eight months. Twenty per cent noted considerable improvement of their symptoms for from six to twenty-four months. Fifteen per cent had moderate improvement from six to seventeen months, and 25 per cent showed no improvement.

In 10 of 13 improved patients who had electrocardiographic studies before and after treatment, the tracing was found partly or completely normalized after irradiation of the suprarenals.—*G. W. Chamberlin.*

JOHNSTON, ZOE A. Treatment of radiation reactions following 200 kv. therapy. *Radiology*, Aug., 1940, *35*, 192–197.

The author considers the general reaction to irradiation known as irradiation sickness and the local skin reactions.

Many remedies have been used for irradiation sickness among which liver extract has become very popular. The effects are not as satisfactory when the extract is given by mouth as when it is given intramuscularly or intravenously. The author has had good results in some cases from the use of liver therapy. It has also been suggested that irradiation sickness is caused by an

avitaminosis and that vitamin B_1 should be given. In the author's own work vitamin B_1 seems to have given the most relief to her patients. In extreme cases vitamin B_1 with the addition of small doses of nembutal has given good results.

With regard to skin reactions, patients should be warned not to apply any medication to the irradiated part. The author recommends the use of a lotion containing zinc oxide or calamine. If the reaction is severe and the patient cannot sleep sitz baths may be used for pelvic cases and ice bags for other parts of the body and a mild sedative given. Dry powder—stearate of zinc—may be used. These reactions all heal unless overdosage has been used, in which case deep ulcers may form. The late reactions are telangiectasis or fibrosis. In the former the electric needle may be used, or if a large area is affected plastic operation may be necessary.

In the discussion Dr. Goin said that the multiplicity of remedies used in radiation sickness is evidence that not much is known about it. It is probable that vitamin deficiency is one cause of irradiation sickness. Many of the patients are suffering from cancer and are undernourished. Vitamin B_1 relieves these patients. But there must be other causes and in a small group of cases he has found that the sickness was due to a decrease in the carbon dioxide combining power of the blood plasma. These patients have been relieved by the intravenous administration of a "molar" solution of sodium lactate. A molar solution of a substance is made by dissolving the molecular weight of the substance in grams in 1000 cc. of water.—*Audrey G. Morgan.*

Chamberlin, George W., Payne, Franklin L., and Stevens, Lloyd W. Post-renal anuria following roentgen therapy for pelvic tumors. *Radiology*, Sept., 1940, *35*, 346–349.

Post-renal anuria means an anuria the source of which is distal to the kidneys. A case is described in a colored woman twenty-seven years old who came for treatment for numbness of the thighs and intense pain in the back and thighs. A diagnosis of retroperitoneal cancer was made from the roentgen examination and roentgen treatment given: 200 kv., 20 ma., 50 cm. skin-target distance, 0.5 mm. copper plus 1 mm. aluminum filter. Half-value layer 1.06 mm. copper. Daily dose June 2 to 10, 99 to 220 r. Total dose measured in air 418 r×3. The masses in the pelvis grew larger and on June 10 the patient became anuric and remained so for eight days, after which there was a slight excretion of urine for the two days before her death.

There were two tumors in the broad ligaments not connected with the uterus or the walls of the pelvis. There was hydronephrosis of both kidneys and both ureters were dilated with clear urine. The tumors were evidently neurogenic but it was impossible to make a more definite classification.

The irradiation evidently caused enough edema of the tumor to obstruct both ureters. Anuria of eight days' duration is not unusual especially in cases in which the kidneys have not been diseased. Intravenous urography should have been done for the purpose of studying the exact condition of the urinary tract before roentgen treatment was given.—*Audrey G. Morgan.*

Moratti, Antonio. Sulla radioterapia preoperatoria del cancro della mammella. (Preoperative radiation therapy of cancer of the breast.) *Radiol. med.*, Oct., 1940, *27*, 783–794.

The author discusses 25 cases of cancer of the breast given preoperative radiotherapy between 1921 and 1938. A table is given showing the details of the treatment and results. When the report was written the average time since the beginning of treatment was three years, the shortest time five months and the longest more than seventeen years. Two of the patients, or 8 per cent, were in the first stage, 9, or 36 per cent, in the second stage and 14, or 56 per cent, in the third stage according to Portmann's classification.

The treatment was with roentgen rays except in one case in which 3 mg. radium was applied for ninety-six hours; in another case in addition to 2,000 r roentgen treatment 25 mg. radium was applied for twenty-five minutes the day before operation. The tension used was 200 to 300 kv. In the first and second stages the breast and axillary region were irradiated, in the third stage the supraclavicular region also and in cases of very large tumor in the third stage a posterior irradiation was given also. The average doses were 2,400 to 2,800 r per field, anticathode-skin distance 50–60 cm., filter 2 mm. copper and 2 mm. aluminum; daily irradiations.

Among the 25 patients 20 were operated on in the second to third month after the beginning of irradiation. At least three weeks should elapse

between the end of roentgen treatment and the operation.

It has been claimed that the delay in operation entailed by roentgen therapy is dangerous and that the irradiation makes the operation more difficult. In this series there was no difficulty in operation except that perhaps in some cases hemostasis was somewhat more difficult. It has also been claimed that roentgen irradiation injures the lung tissue and tends to cause pleuropneumonia. The author found there was no danger of lung complications if lung disease was excluded before operation and careful roentgen technique was used.

Histopathological examination showed regressive changes in the tumor tissue after irradiation. Hard, scirrhous cancers were less affected than other forms. Generally, these changes became manifest three weeks after irradiation, as shown by serial biopsies in one case.

Fourteen patients were found free of recurrence after an average interval of more than four years after treatment. Both of the patients in the first stage were living and free of recurrence, among the 9 of the second stage there had been 1 recurrence, or 22.22 per cent, and among the 14 of the third stage there had been 10 recurrences, or 71.43 per cent. This is better than the figures quoted from other authors for operation alone. The time that elapsed between operation and recurrence was also longer than in the statistics reported for operation alone.

The number of cases reported is small, but they show that the dangers attributed to preoperative irradiation are not real; preoperative irradiation was followed by satisfactory results in the first and second stages and even in the third stage the tumors were sometimes rendered operable. Therefore the method is worthy of more extended use.—*Audrey G. Morgan.*

GOIN, L. S., HOFFMAN, E. F., and CRANE, J. J. Treatment of certain types of bladder tumor by contact x-ray therapy (Chaoul technique). *J. Urol.*, Dec., 1940, *44*, 847–849.

The cardinal symptom of cancer of the bladder is hematuria. Every case of hematuria demands a cystoscopic examination. The majority of malignant bladder tumors occur in the region of the trigone and are not resectable. Small papillomatous growths may be completely cured by resection or transurethral fulguration. These are classified by the Registry of the American Urological Association as Grade 1 carcinoma. Excluding this group and cancers in the fundus and on the lateral walls total cystectomy is the only surgical treatment for cancer of the bladder. Total cystectomy is a serious procedure with a 50 per cent primary mortality.

The authors suggest a combination of surgery and contact roentgen therapy. They use a Philips Metalix contact tube at 50 kv. and a 2 cm. target-skin distance. The output of this machine is 7,420 r per minute without a filter and 1,278 r with a filter of 1 mm. Al. At 1 cm. the depth dose is only 30 per cent. The approach to the tumor is possible through a cystostomy. They administerd doses of 30,000 r to an area 3 cm. in diameter with fractional doses of 8,000 r given weekly. Their series includes 17 cases, 1 of whom died of intercurrent infection and 2 of whom were treated too recently to be considered in their statistics. The remaining 14 cases had apparent cures of the primary disease. The elapsed time since treatment has only been from two to sixteen months which is hardly sufficient to permit any conclusions to be drawn. —*R. M. Harvey.*

BARRINGER, BENJAMIN S. End-results of carcinoma of the bladder treated by radium. *Surg., Gynec. & Obst.*, Feb. 15, 1940, *70*, 598–600.

This author's series includes 228 consecutive cases of cancer of the bladder treated by radium. Both the cystoscopic and suprapubic methods have been used. Whenever possible, cystoscopic examination was preferred. Many of the cases were those of carcinoma involving the bladder near the urethra or near one or both ureters. These regions are favorable for cystoscopic manipulation. In computing the five year results the author used 188 determinate cases. Of these cases 71, or 37.8 per cent, were well for five years; 117, or 62.2 per cent, died of cancer. The author seems to favor radon seed implantation for the treatment of carcinoma of the bladder. —*G. W. Chamberlin.*

PEARSE, R., and MCCOMB, R. A. The treatment of infiltrating tumors of the bladder. *Canad. M. Ass. J.*, Aug., 1940, *43*, 106–110.

The authors show that in their experience the results of partial resection of the bladder for infiltrating carcinoma produces less than 12 per cent survival. Their results with diathermy and radon through a cystotomy opening are better than by resection or by diathermy without radon.

Ureterosigmoid anastomosis followed by cystectomy is advisable if there are no demonstrable metastases, no pyelonephritis and the general condition of the patient is good.—*G. W. Chamberlin.*

Perussia, Felice. Insuccessi e recidive dopo plesioroentgenterapia di tumori maligni. (Failures and recurrences after plesioroentgen therapy of malignant tumors.) *Radiol. med.*, Nov., 1940, *27*, 861–864.

There is a natural tendency to emphasize successes in reporting treatment. But the reporting of failures may be of equal value by helping to avoid future errors and learning how to adapt treatment to the individual case.

The author therefore reports the immediate failures and the late recurrences among the cases of plesioroentgen therapy of malignant tumors at the Radiological Institute of the University of Milan from 1935 to the end of 1939. A total of 267 cases were treated in this way with immediate cure in 261, or 97.7 per cent, and failure in 6, or 2.3 per cent. These were mostly skin cancers; some of them were cancers of the mucous membrane of the mouth or nose, or of the cornea. Among the 261 cured cases the cures were permanent in 234, or 89.6 per cent, and there was recurrence in 27, or 10.4 per cent. Among these 27 cases of recurrence, 25 were in tumors of the skin and 2 in tumors of the lip. Some of these patients had been treated before and the technique had not been perfect in some of the preceding treatments. Among these 27 recurrences 9 were again cured by being retreated. It is worth noting that 8 of these cured cases were among the 13 that had not been treated before they came to the author, while only 1 was among the 14 that had been treated elsewhere by other methods. The histopathological nature of the tumors did not appear to have much effect on the results of treatment. The one exception to this was the melanoblastomas which gave a high percentage of recurrence. Certain localizations of the tumor also appeared to be particularly unfavorable, such as the angle of the eye, the ala nasi and the auricular region.—*Audrey G. Morgan.*

Paltrinieri, G., and Dossena, G. Adenocarcinoma bilaterala dell'ovaio inoperabile, trattato con successo con la radioterapia. (Bilateral inoperable carcinoma of the ovaries successfully treated with radiotherapy.) *Radiol. med.*, Nov., 1940, *27*, 879.

A woman of thirty-six came for treatment for bilateral tumor of the ovary. Two large masses adherent to the intestines and absolutely inoperable were found. Biopsy showed adenocarcinoma. The patient was in bad general condition and cachectic. She was treated first with two radium sounds introduced into the vagina, each containing 25 mg. radium. The sounds were pushed as far to the sides as possible with gauze tampons. After four days the total charge of radium was reduced to 5 mg. on each side. In eight days a dose of 66.48 mcd was given. There was a marked reaction and a reduction in size of the tumor, especially on the left side.

After twenty-five days roentgen treatment of the pelvis was begun from six fields, two in front, two in the back and two lateral. A dose of 1,250 r was given over each field, making a total dose of 7,500 r in forty-two days, with a focal distance of 40 cm. for the anterior and posterior fields and 30 cm. for the lateral ones, 180 kv., 4 ma., 300 r per field until 900 r was given, then decreasing to 200 and 150 r per treatment, with a filter of 1 mm. copper and 0.5 mm. aluminum.

The patient was discharged in good condition; the tumor was reduced in size and finally disappeared; the patient rapidly gained 12 kg. in weight. At the end of a year she is still in good condition. This is a brilliant result for so large and inoperable a tumor of such a radioresistant type.—*Audrey G. Morgan.*

Stone, Robert S., Lawrence, John H., and Aebersold, Paul C. A preliminary report on the use of fast neutrons in the treatment of malignant disease. *Radiology*, Sept., 1940, *35*, 322–327.

Aebersold first succeeded in collimating fast neutrons into beams so that they could be used in the treatment of cancer. An illustration is given showing a horizontal section of the cyclotron with collimating device and treatment cubicle.

The unit of measurement of neutron units is called n. It is an arbitrary measurement used to designate the quantity of neutrons that discharges a Victoreen r meter to the same extent as 1 r of roentgen rays. The dose of neutrons to be used in practice was arrived at by a study of the comparative effects of roentgen rays and neutrons on biologic objects such as *Drosophila* eggs, wheat seedlings and fern spores. It was decided that the number of neutron units that could be used safely on a patient is about one-fourth the number of roentgens of 200 kv. rays

that would be required for a given erythema.

Twenty-four patients were treated. The treatments given were single erythema doses. They were not even skin tolerance doses and were not fractionated. The patients were all ones who had no chance of being cured with radium, roentgen rays or surgery. The results were promising enough to warrant a more thorough trial of this new method of treatment.

In the fall of 1939 a new cyclotron was completed which can be used for fractional treatments. It is too soon to report the results of this treatment but the immediate responses are greater than before and the general reactions not so severe.—*Audrey G. Morgan.*

MISCELLANEOUS

GREENBAUM, FREDERICK R., and PETERS, ALLEN F. A new organic thorium compound for x-ray diagnostic purposes. *Radiology*, July, 1940, *35*, 45–50.

A description is given of the method of preparing sodium thorium tartrate and a discussion of the physical and chemical theories which led to its adoption as a contrast medium for examination of the gastrointestinal tract. A possible structural formula of the compound is suggested. High molecular solutions such as 50 per cent sucrose or 50 per cent dextrose screen out the gamma-ray activity of radioactive thorium compounds to some extent. The radiopacity of the sodium tartrate is determined by means of very sensitive roentgen film.

Experiments on rabbits showed that when sodium thorium tartrate is given by mouth for sixty days it is non-toxic. These animals did not show any changes in the bones. The compound when given by mouth did not appear to have any cumulative action and was eliminated rapidly. Rabbits that were given 10 and 20 cc. sodium thorium tartrate by mouth and roentgen films made at once showed a clear, distinct outline of the greater and lesser curvatures of the stomach including the rugae. The roentgenogram obtained in this way, particularly after the 20 cc. dose, was better than the film obtained with barium sulphate.—*Audrey G. Morgan.*

HENSHAW, PAUL S., and GOLOMB, I. M. Responses of *Drosophila* pupae to x-rays. *Radiology*, June, 1940, *34*, 721–730.

The authors investigated the value of *Drosophila* pupae as test objects for quantitative radiobiological work. As a supplement to this investigation they studied the relation between radiosensitivity, developmental activity and respiratory rate at various stages during the pupal period. They give curves showing their results.

They found that for the first eighteen hours the organisms maintain a strikingly uniform radiosensitiveness but that after that their resistance increases very rapidly. They divided their development into three stages and found that there was a positive correlation between the rate of oxygen uptake and developmental activity but that there was no correlation between either of these and radiosensitiveness. The general shape of the curve for oxygen uptake during the pupal period was not changed materially when lethal doses of radiation were given early in the period.

Drosophila pupae are recommended as good test material for radiobiologic studies because they are easy to obtain at all seasons, they are small, with a diameter of about 1 mm. and a length of about 2.5 mm., they resist drying, they are relatively radiosensitive, about 50 per cent being killed by a dose of 2,700 r, and they give results which can be reproduced with only slight variation from day to day.—*Audrey G. Morgan.*

WENK, PAUL. Messungen in bezug auf den Strahlenschutz des Bedienungspersonals bei der Siemens-Röntgenbombe. (Measurements with reference to protection of the personnel from irradiation in using the Siemens roentgen bomb.) *Strahlentherapie*, 1940, *68*, 343–346.

The author illustrates the Siemens roentgen bomb used in the University Gynecological Clinic at Erlangen. The tube is covered with a layer of leaded rubber 6 mm. thick. The bottom of the treatment table is also covered with a layer of lead 3 mm. thick. The assistant who is giving the treatment must also be protected not only from direct radiation but from scattered radiation from the air and from the body of the patient, for every body that is struck by very soft rays gives off a secondary radiation.

Measurements of the scattered radiation were made with an ionization chamber at a distance of 2.5 m. from the exit of the rays at a height of 1.5 m. from the floor, for different focus-skin distances and different lengths of tube. A table

of these measurements is given. If the table at which the assistant sits is located at a distance of 3 meters from the patient and protected in front with a wall of lead 3 to 4 mm. thick or an equivalent thickness of leaded glass, the assistant can safely work in the same room with the patient. This gives the patient a feeling of confidence that he does not have if he is alone in unfamiliar surroundings and under treatment with a new and seemingly mysterious apparatus.—*Audrey G. Morgan.*

Teschendorf, Hans J. Über Röntgenstrahlenreaktionen am Kaninchenohr unter besonderer Berücksichtigung von Intensitätsänderungen. (Reactions of the rabbit's ear to roentgen irradiation, with special reference to changes in intensity.) *Strahlentherapie*, 1940, *68*, 304–342.

The author has found the rabbit's ear an especially good object for the study of reactions to the roentgen rays because its irradiation with large doses does not have any effect on the animal's general condition. The ear is so thin that scatter is practically negligible and both the outer and inner sides of the ear can be examined as the light shines through it; in this way the very earliest reactions can be tested, and their every stage followed up.

The reactions vary in different races of rabbits and with changes in season and temperature. In the summer months and with high temperatures sensitiveness to the rays is increased. Races with small ears and consequently less well developed vascular systems are not very sensitive to irradiation. Variations in the total reaction to the rays are brought about by varying sensitiveness of the blood vessels.

In order to get a uniform material for examination races of rabbits with large ears were bred. But animals even of the same litter and the same color show differences in sensitiveness, so comparative radiobiological experiments cannot be made on different animals but they can be made on the same animal.

A study was made of the different degrees of reaction to the rays; erythema, pigmentation, epilation, reaction of the epidermis, reparative processes and the late changes after a single irradiation; these were examined with doses of 500, 1,000, 1,500, 2,000 and up to 5,000 r. The highest tolerated dose with a single irradiation (36 r/min.) was 2,000 r; changes in sensitiveness due to season and temperature had to be taken into consideration.

Histological examinations after the reaction had subsided showed changes in the hair papillae and the epidermis, in pigmentation and in the sebaceous glands. The effect of irradiation on the pigment of the epidermis and the hair is particularly dependent on the dose used. Pigment formation in the epidermis is at first stimulated and later pigmentation of the epidermis and of the hair is inhibited.

In the second part of the article the effect of changes in intensity with the same dose in a single irradiation is considered. With intensities of from 30 to 1,300 r/min. no differences could be seen in the course of the reaction or in the late changes. In comparing intensities of 7 and 1,300 r/min. slight changes could be seen in the course of the reaction but the end-results were the same.

Studies with divided doses showed that intensity is of secondary importance but that the size of the partial doses and the total dose was the decisive factor in the degree of the reaction. The examinations also showed that the course of the reaction was not changed by varying the half-value layer from 0.25 to 1.0 mm. copper. Only the size of the dose is important.

The examinations help to clear up the question of how well irradiations of high intensity can be borne, which is of great interest since the introduction of high voltage roentgen therapy. —*Audrey G. Morgan.*

Luther, Wolfgang. Weitere Untersuchungen über das Verhalten der Zellteilungen in der Haut röntgenbestrahlter Salamanderlarven. (Further study of cell division in the skin of salamander larvae irradiated with roentgen rays.) *Strahlentherapie*, 1940, *68*, 185–205.

The author irradiated the cornea and surrounding skin of salamander larvae. Technique: 180 kv., 15 ma., filter 0.5 mm. copper, focus-skin distance 40 cm. He made two series of experiments, in one of which a single dose of 550 r was used and in the other fractional doses. He gives curves showing the effect of these types of irradiation on mitoses and the disturbance of the chromosomes after division, which is called the secondary effect.

He found that with a single irradiation of 550 r the mitosis curve was flat, that is that the action of the rays almost inhibited the occur-

rence of mitoses and that the ones that were produced were all abnormal. The picture with fractional irradiation was quite different. The injury to mitosis was greatly decreased by dividing the dose. The smaller the individual dose and the longer the interval between doses the greater the number of mitoses. The form of the curve with this type of irradiation is determined by the injury of the chromosomes. It is wave-like and shows four waves: (*a*) a first period of minimum mitoses; (*b*) a first period of maximum mitoses (chief reaction). The number of mitoses in this period never reached normal and all the mitoses were pathological; (*c*) a second period of minimum mitoses. This period of nuclear disintegration probably corresponds to the time when the cells injured by the secondary effect divide for the second time. During this period many dead and disintegrating nuclei appear. This second minimum is partially covered by (*d*) the second period of maximum mitoses or period of regeneration during which the few cells that have remained intact rapidly increase and replace the destroyed tissue. This period lasts for months and during it the number of mitoses is greatly increased.

The number of mitoses in the tissue at the time of the second irradiation does not have any effect on the reaction to the rays. Irradiations in periods (*a*) and (*b*) have just the same effect. Some authors have observed a more intense reaction in period (*b*) and attribute it to the fact that toward the end of this period the increase of the cells that have remained uninjured begins. A second irradiation at this time inhibits this increase so that regeneration takes place more slowly and the injured cells disintegrate more rapidly.

An intense action can be expected from fractional irradiation only when the individual doses are large enough to destroy the regenerating cells completely. An experiment is described in which recovery of the tissue took place even during irradiation because of the use of too small doses and too long intervals between them. This experiment shows that in young cells that have not suffered any injury of the chromosomes the irradiation of former generations has little or no effect. The normal cells of the phase of regeneration behave as if there had been no irradiation.

The duration of the individual waves of the reaction depends on the kind of tissue. At a time when almost all the epidermal cells of the skin have become normal again mitoses showing an intense secondary effect are still found in the connective tissue cells of the cornea.—*Audrey G. Morgan.*

QUIMBY, EDITH H., and LAURENCE, GEORGE C. The Radiological Society of North American Standardization Committee, Technical Bulletin No. 1. *Radiology*, Aug., 1940, *35*, 138–159.

This Bulletin defines the technical terms used in roentgenology, some of which have been changed in conformity with new methods and recent knowledge. It gives a description of the instruments and apparatus used in modern radiology, discusses methods of measurement and gives tables of skin and tissue doses under different conditions. Copies of the Bulletin may be obtained from the Secretary, D. S. Childs, M.D., 607 Medical Arts Building, Syracuse, N. Y., at a small cost.—*Audrey G. Morgan.*

GILARDONI, ARTURO. La radiografia al milionesimo di secondo. (Roentgenography with an exposure time of millionths of a second.) *Radiol. med.*, Dec., 1940, *27*, 944–948.

The author describes and illustrates an apparatus which he devised in 1938 for taking roentgenograms with a very brief exposure time. This was used in collaboration with Prof. Cignolini for regmography. He succeeded in reducing the time of exposure to a thousandth of a second. The Philips firm has now announced an apparatus for taking roentgenograms with an exposure time of five millionths of a second. Gilardoni says that the principle is the same as that used by him. With the Philips apparatus only roentgenograms of a hand at a short focal distance have been taken while he has succeeded in making a roentgenogram of the lungs at a distance of 1.50 meters.—*Audrey G. Morgan.*

GOLDFEDER, ANNA. Further studies on the effects of irradiation on proliferation and metabolic processes of normal and malignant tissues. IV. Effects produced by different dosage rates of x-ray radiation on the proliferation of various tissues grown *in vitro*. *Radiology*, Aug., 1940, *35*, 210–228.

It has never been definitely determined whether high dosage rates for a short time or low dosage rates for a long time produce the most marked effects. The author tries to contribute to a solution of this problem by describing her experiments in irradiating the kidneys

and spleens of rats one to two days old, mouse sarcoma 180 that had been growing in the animal body eight to ten days and the hearts of embryo chicks eight days old. Three different dosage rates were used, 234 r/min., 936 r/min. and 10,000 r/min. The details of the experiments are described and tables given showing the results.

With all these tissues the results depended on the two factors of time of irradiation and dosage rate. Therefore the proper combination of the two factors must be used to produce the best results. Figures for the various exposure times and dosage rates are given. Roentgen rays have a selective action on the proliferation of various tissues; the critical dosage levels varied for the different kinds of tissue used. Liquefaction of the nutritive medium was produced by enzymes of the dead cells.

The importance of the time factor in irradiation suggests that there are sensitive phases during cell division and therefore a smaller dosage rate with longer exposure would increase the probability of direct hits and thereby decrease the dosage necessary for the production of a given biological effect. This view is supported by the results recorded. Irradiation within certain dosage levels has an effect not only on the viability but also on the reproductive capacity of the cells.

A larger dose is required to prevent proliferation of tissue than to inactivate the nutritive medium. A much higher dose is required to affect the metabolic processes of various tissues than to prevent proliferation. For example, a dose of 300,000 r applied for thirty minutes using a dosage rate of 10,000 r/min. did not affect the oxygen intake or the aerobic glycolysis of rat kidney, although a dose of 150,000 r of the same type of radiation prevented the proliferation of this tissue.

The doses of roentgen rays required to prevent proliferation in these experiments is much higher than those tolerated in vivo. But the elimination of the blood, lymph, nerves and other systems of the living body makes it possible to make a more accurate study of the factors that control growth processes. The effects produced by different doses and dosage rates on tissues in vitro, such as the relation of the time intensity factor, the selective action of the rays, the latent period and the liquefaction of the nutrient medium could not be determined by studies in vivo. But they show the actual effects produced by radiation on the physiologic processes and therefore bring out facts that can be applied practically.—*Audrey G. Morgan.*

Koehring, Vera. The additive effects of radon and neutral red upon *Chaos chaos*. *Radiology*, Aug., 1940, *35*, 229–235.

Cultures of the ameba, *Chaos chaos*, were stained with neutral red and irradiated with radon needles at the same time. Marked changes were brought about which are illustrated on a plate showing comparative drawings of normal and stained, irradiated amebae. The changes were more marked than those produced by irradiation alone or by preliminary staining followed by irradiation.

Neutral red is a stain that has been used so much clinically that it is known to be non-toxic. It may therefore prove of value in increasing the radiosensitivity of cells before they are irradiated.—*Audrey G. Morgan.*

Piergrossi, Aldo. Sulla radiografia a foro stenopeico dell'irradiamento secondario degli oggetti. (Roentgenography of the secondary radiation of objects by means of the pinhole camera.) *Radiol. med.*, Sept., 1940, *27*, 673–686.

Non-luminous objects are visible because of the light which is diffused or reflected from their surface. When roentgen rays fall on an object they also produce a large amount of secondary radiation which is diffused into the surrounding air and which is similar in some respects to diffuse irradiated light. But these secondary roentgen rays, like primary roentgen rays, are invisible. Nor can they be photographed by ordinary methods. The author, however, describes a method of photographing them by means of a pinhole camera. This gives a direct image of the object irradiated as it would appear if roentgen rays were visible.

He used a wooden box with all its walls lined with lead plates 3 mm. thick. There was a hole 2 mm. in diameter in one wall and the film was stretched on the opposite wall. The clearness of the image depends on the size of the hole and the distance from the focus to the film. This distance in his experiments was 10 cm. The apparatus is illustrated and photographs given of various objects photographed in this way, including metal plates, teeth, bones, the body of a rabbit, etc. The primary ray can be seen in a radiotransparent medium as a beam of light

can be seen when it passes through the dust in the air. This was illustrated by a "phantom" consisting of a box of rice.

The image obtained by secondary roentgenography, as the author names this method, depends on the nature of the primary radiation and the filtration of the secondary radiation. The conditions involved are extremely complex and will require further experimentation with perfected apparatus.—*Audrey G. Morgan.*

Lenzi, Mario. Una lente per raggi Roentgen —Prime esperienze per una sua applicazione alla terapia. (A lens for roentgen rays—first experiments in its application to treatment.) *Radiol. med.*, Dec., 1940, *27*, 933–944.

In 1930 Prof. Pierucci said that he had succeeded in collecting a considerable amount of radiant energy from a roentgen tube in a given area, determined accurately not only in extent but in depth. He had used a "collector" made up of a number of crystalline cylinders. The author has been doing work on this subject in collaboration with Prof. Pierucci. He uses the word lens, instead of collector, and describes and illustrates the apparatus used and discusses the technique. He used a mica and a graphite lens.

He discusses the possibility of utilizing such lenses in roentgen diagnosis and treatment and concludes that this may not be impossible as they have succeeded in concentrating considerable amounts of roentgen energy on a given object.—*Audrey G. Morgan.*